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(54) Title: SUBSTITUTED BENZENE-FUSED HETERO- AND CARBOCYCLICS AS NEUROKININ ANTAGONISTS

(57) Abstract

Compounds represented by structural formula (1), or a pharmaceutically acceptable salt thereof, wherein: A^1, A^2, A^3 and A^4 are methylene, -CH= or -NH-, all optionally substituted, or -N=, -O-, -S(O)$_e$-, -C(O)- or a bond; E is phenyl or heteroaryl; W is cycloalkyl, aryl, heterocycloalkyl or heteroaryl; R^5, R^7, R^9, R^{11}, R^{12} and R^{14} are H, alkyl, phenyl, benzyl, -CF$_3$ or -C$_2$F$_5$; R^{10} is H or alkyl; R^6 and R^8 are R^5, or optionally substituted alkyl further substituted by -OR^{11}, -NR^{11}R^{12}, -SH, -S(O)$_e$R^{13}, -CO$_2$R^{11}, -OC(O)R^{11}, -CONR^{11}R^{12}, -COR^{11} or -NR^{11}C(O)R^{12}; R^{13} is alkyl, phenyl, benzyl, -CF$_3$ or -C$_2$F$_5$; Q is a bond, -C(O)-, -NR^{17}-, -(C(R^9)(R^{10}))-, -O-,

-S(O)$_e$-, -C(X)NR^{11}-, -N(R^{11})C(X)-, -N(R^{11})SO$_2$- or -SO$_2$N(R^{11})-; R^{17} is H, alkyl, -S(O)$_e$R^{13}, -COR^{11}, -CO$_2$R^{13}, -CONR^{11}R^{12}, allyl, -(C$_1$-C$_6$ alkyl)-CH=CH$_2$, phenyl or benzyl; X is =O, =S or =N(R^{12}); Y^1 is -(C(R^9)(R^{10}))$_m$-, -G-(C(R^9)(R^{10}))$_m$- or -(C(R^9)(R^{10}))$_m$-G-; G represents formulas (a); (b); (c); (d); (e) or (f), with certain provisos; T is H, aryl, heterocycloalkyl, heteroaryl, cycloalkyl, -OR^{11}, -N(R^{11})(R^{12}), -COR^{11}, -CO$_2$R^{11}, -CON(R^{11})(R^{12}), -S(O)$_e$R^{13}, -NR^{11}CO$_2$R^{13}, -NR^{11}COR^{12}, -NR^{11}CON(R^{12})(R^{14}) or -OC(O)N(R^{11})(R^{12}); V is a bond, -S(O)$_e$-, -O- or -N(Z^2)-, -N(Z^2)C(O)- or -N(Z^2)C(S)-; Y^2 is -(C(R^9)(R^{10}))$_m$-; Z^1 is Z^2, -NR^{11}R^{12}, -OR^{11} or SR^{11}; Z^2 is H, alkyl, phenyl, benzyl, -CF$_3$ or -C$_2$F$_5$; or Z^1 and Z^2 together are -(C(R^9)(R^{10}))$_u$-, wherein u is 1-4; e and n are 0-2; m and p are 0-3; and r and s are 1-4; wherein cycloalkyl, heterocycloalkyl, phenyl, benzyl, aryl and heteroaryl groups are all optionally substituted; methods of treating asthma, cough, bronchospasm, inflammatory diseases, and gastrointestinal disorders with said compounds, and pharmaceutical compositions comprising said compounds are disclosed.
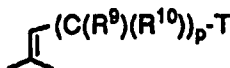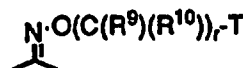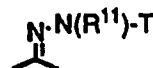
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SUBSTITUTED BENZENE-FUSED HETERO- AND CARBOCYCLICS AS NEUROKININ ANTAGONISTS

BACKGROUND OF THE INVENTION

The present invention relates to a genus of substituted benzene-fused hetero- and carbocyclics useful as antagonists of tachykinin receptors, in particular as antagonists of the neuropeptides neurokinin-1 receptor (NK_1) and/or neurokinin-2 receptor (NK_2) and/or neurokinin-3 receptor (NK_3).

Neurokinin receptors are found in the nervous system and the circulatory system and peripheral tissues of mammals, and therefore are involved in a variety of biological processes. Neurokinin receptor antagonists are consequently expected to be useful in the treatment or prevention of various mammalian disease states, for example asthma, cough, bronchospasm, inflammatory diseases such as arthritis, central nervous system conditions such as migraine and epilepsy, nociception, and various gastrointestinal disorders such as Crohn's disease.

In particular, NK_1 receptors have been reported to be involved in microvascular leakage and mucus secretion, and NK_2 receptors have been associated with smooth muscle contraction, making NK_1 and NK_2 receptor antagonists especially useful in the treatment and prevention of asthma.

Some NK_1 and NK_2 receptor antagonists have previously been disclosed: arylalkylamines were disclosed in U.S. Patent 5,350,852, issued September 27, 1994, and spiro-substituted azacycles were disclosed in WO 94/29309, published December 22, 1994.

SUMMARY OF THE INVENTION

Compounds of the present invention are represented by the formula I
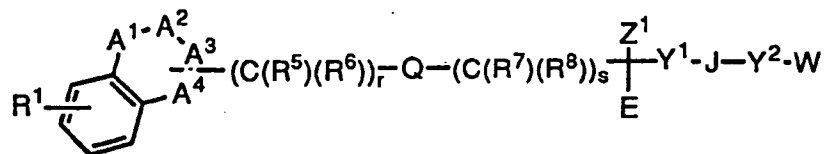
$$A^1\text{-}A^2 \atop \diagdown A^3$$

$$R^1 \overset{\displaystyle}{\underset{\displaystyle}{\bigcirc}} \diagdown A^4 \text{---}(C(R^5)(R^6))_r\text{---}Q\text{---}(C(R^7)(R^8))_s \underset{E}{\overset{Z^1}{\text{---}}} Y^1\text{-}J\text{---}Y^2\text{-}W$$

I

or a pharmaceutically acceptable salt thereof, wherein:

A^1, A^2, A^3 and A^4 are independently selected from the group consisting of -(C(R^2)(R^{10}))-, -(C(R^{2c})(R^{10}))-, -(C(R^2))=, -(C(R^{2c}))=, -NR^{16}-,

5   -N=, -O-, -S(O)$_e$-, -C(O)- and a bond, wherein A^1, A^2, A^3 and A^4, together with the carbon atoms to which they are attached, form a 5- or 6-membered ring, and wherein two adjacent A groups are selected from the group consisting of the following combinations:

-(C(R^2)(R^{10}))-(C(R^2)(R^{10}))-;

10   -(C(R^2)(R^{10}))-(C(R^{2c}))=;

-(C(R^{2c})(R^{10}))-NR^{16}-;

-(C(R^{2c})(R^{10}))-N=;

-(C(R^{2c})(R^{10}))-O-;

-(C(R^{2c})(R^{10}))-S(O)$_e$-;

15   -(C(R^2)(R^{10}))-C(O)-;

-(C(R^2))=(C(R^2))-;

-(C(R^2))=N-;

=(C(R^2))-(C(R^2))=;

=(C(R^2))-NR^{16}-;

20   =(C(R^2))-N=;

=(C(R^2))-O-;

=(C(R^2))-S(O)$_e$-;

=(C(R^2))-C(O)-;

-NR^{16}-N=;

25   -NR^{16}-S(O)$_e$-;

-NR^{16}-C(O)-;

-N=N-;

=N-N=;

=N-O-;

30   =N-S(O)$_e$-;

=N-C(O)-;

-O-S(O)$_e$-; and

-O-C(O)-;

provided that three adjacent A groups do not represent -C(O)-O-C(O)-, -S(O)-O-C(O)- or -S(O)-O-S(O)-, and provided that when an aromatic nitrogen is present in the ring formed by A^1, A^2, A^3 and A^4, the N-oxide can be formed;

E is R^3-aryl or R^3-heteroaryl;

W is R^4-cycloalkyl, R^4-aryl, R^4-heterocycloalkyl or R^4-heteroaryl;

R^1, R^3 and R^4 are independently 1-3 substituents independently selected from the group consisting of H, halogeno, C_1-C_6 alkyl, -CF_3, -C_2F_5, -OR^{11}, -COR^{11}, -CO_2R^{11}, -$CON(R^{11})(R^{12})$, -$N(R^{11})(R^{12})$, -$N(R^{11})COR^{12}$, -SH, -$S(O)_eR^{13}$, -$OC(O)R^{11}$, -$OC(O)N(R^{11})(R^{12})$, -$NR^{11}CO_2R^{13}$, -$NR^{11}C(O)N(R^{12})(R^{14})$, R^{15}-phenyl, R^{15}-benzyl, -NO_2, -$NR^{11}S(O)_2R^{13}$ and -$S(O)_2NR^{11}R^{12}$; or adjacent R^1, R^3 or R^4 substituents can form a -O-CH_2-O- group;

R^2 is independently selected from the group consisting of R^{2a}, R^{2b} or R^{10}; and R^{2c} is independently selected from the group consisting of R^{2a} and R^{10}; wherein R^{2a} is selected from the group consisting of -CF_3, -C_2F_5, -COR^{11}, -CO_2R^{11}, -$CON(R^{11})(R^{12})$, R^{15}-phenyl and R^{15}-benzyl; and R^{2b} is selected from the group consisting of halogeno, -OR^{11}, -NO_2, -$N(R^{11})(R^{12})$, -$N(R^{11})COR^{12}$, -SH, -$S(O)_eR^{13}$, -$OC(O)R^{11}$, -$OC(O)N(R^{11})(R^{12})$, -$NR^{11}CO_2R^{13}$, -$NR^{11}C(O)N(R^{12})(R^{14})$, -$NR^{11}S(O)_2R^{13}$ and -$S(O)_2NR^{11}R^{12}$; provided that from any combination of ring members A^1, A^2, A^3 and A^4 comprising R^2 and R^{2c}, no more than one substituent can be selected from R^{2a} and no more than one substituent can be selected from R^{2b};

R^5, R^7, R^9, R^{11}, R^{12} and R^{14} are independently selected from the group consisting of H, C_1-C_6 alkyl, R^{15}-phenyl, R^{15}-benzyl, -CF_3 and -C_2F_5;

R^6 and R^8 are independently selected from the group consisting of R^5, -$(C(R^9)(R^{10}))_n$-OR^{11}, -$(C(R^9)(R^{10}))_n$-$NR^{11}R^{12}$, -$(C(R^9)(R^{10}))_n$-SH, -$(C(R^9)(R^{10}))_n$-$S(O)_eR^{13}$, -$(C(R^9)(R^{10}))_n$-CO_2R^{11}, -$(C(R^9)(R^{10}))_n$-$OC(O)R^{11}$, -$(C(R^9)(R^{10}))_n$-$CONR^{11}R^{12}$, -$(C(R^9)(R^{10}))_n$-COR^{11} and -$(C(R^9)(R^{10}))_n$-$NR^{11}C(O)R^{12}$, provided that when Q is a heteroatom, R^6 and R^8 cannot be -OR^{11}, -$OC(O)R^{11}$, -$N(R^{11})COR^{12}$, -$NR^{11}R^{12}$, -SH or -$S(O)_eR^{13}$ on adjacent carbon atoms;

R^{10} is independently selected from the group consisting of hydrogen and C_1-C_6 alkyl;

R^{13} is independently selected form the group consisting of C_1-C_6 alkyl, R^{15}-phenyl, R^{15}-benzyl, -CF_3 and -C_2F_5;

R^{15} is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy or halogeno;

Q is a bond, -C(O)-, -NR^{17}-, -(C(R^9)(R^{10}))-, -O-, -S(O)$_e$-, -C(X)NR^{11}-, -N(R^{11})C(X)-, -N(R^{11})SO_2-, -SO_2N(R^{11})- or -N+(R^{11})(R^{17})-;

R^{16} and R^{17} are independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, -S(O)$_e$$R^{13}$, -$COR^{11}$, -(CH$_2$)$_m$-$CO_2R^{13}$, -$CONR^{11}R^{12}$, alkenyl, -$R^{15}$-phenyl and R^{15}-benzyl;

X is =O, =S or =N(R^{12});

Y^1 is -(C(R^9)(R^{10}))$_m$-, -G-(C(R^9)(R^{10}))$_m$- or -(C(R^9)(R^{10}))$_m$-G-;

G is

, provided that when m is 0, R^2 is H, C_1-C_6 alkyl, -CF_3, -C_2F_5, -COR^{11}, -CO_2R^{11}, -CON(R^{11})(R^{12}), R^{15}-phenyl or R^{15}-benzyl;

, provided that when p is 0, T is not OH or -$NR^{11}R^{12}$;

, provided that when r is 1, T is not OR^{11} or -$NR^{11}R^{12}$; or

, provided T is not -OR^{11}, -N(R^{11})(R^{12}), -S(O)$_e$$R^{13}$, -$NR^{11}CO_2R^{13}$, -$NR^{11}COR^{12}$, -$NR^{11}CON(R^{12})(R^{14})$ or -OC(O)N(R^{11})(R^{12});

T is H, R^{15}-aryl, R^{15}-heterocycloalkyl, R^{15}-heteroaryl, R^{15}-cycloalkyl, -OR^{11}, -N(R^{11})(R^{12}), -COR^{11}, -CO_2R^{11}, -CON(R^{11})(R^{12}), -S(O)$_e$$R^{13}$, -$NR^{11}CO_2R^{13}$, -$NR^{11}COR^{12}$, -$NR^{11}CON(R^{12})(R^{14})$ or -OC(O)N(R^{11})(R^{12});

J is a bond, -S(O)$_e$-, -O- or -N(Z^2)-, -N(Z^2)C(O)- or -N(Z^2)C(S)-; and when G is -C(R^2)H-, J can also be -N(Z^2)C(O)O- or -OC(O)N(Z^2)-;

Y^2 is -(C(R^9)(R^{10}))$_m$-;

Z^1 is H, C_1-C_6 alkyl, R^{15}-phenyl, R^{15}-benzyl, -CF_3, -C_2F_5, -$NR^{11}R^{12}$, -OR^{11} or SR^{11}; Z^2 is H, C_1-C_6 alkyl, R^{15}-phenyl, R^{15}-benzyl, -CF_3 or -C_2F_5; provided that when Y^1 is -(C(R^9)(R^{10}))$_m$- and m is 0, Z^1 is not -$NR^{11}R^{12}$, -OR^{11} or -SR^{11}; or Z^1 and Z^2 together are -(C(R^9)(R^{10}))$_u$-,

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wherein u is 1 to 4, and wherein with the atoms to which they are attached, form a 4 to 8 membered ring;
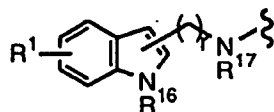
     e and n are independently 0, 1 or 2;

     m and p are independently 0, 1, 2 or 3; and

     r and s are independently 1, 2, 3 or 4.

Preferred are compounds of formula I wherein W is R^4-cycloakyl, R^4-aryl or R^4-heteroaryl. Preferred R^1, R^2, R^3 and R^4 substituents are H, halogeno, C_1-C_6 alkyl, $-CF_3$, $-OR^{11}$, $-COR^{11}$, $-CO_2R^{11}$, $-CON(R^{11})(R^{12})$ and $-N(R^{11})(R^{12})$. R^5, R^7, R^9, R^{11}, R^{12} and R^{14} are preferably independently H, C_1-C_6 alkyl or $-CF_3$. R^6 and R^8 are preferably independently hydrogen, $-(C(R^9)(R^{10}))_n-OR^{11}$, $-(C(R^9)(R^{10}))_n-NR^{11}R^{12}$, $-(C(R^9)(R^{10}))_n-SH-$, $(C(R^9)(R^{10}))_n-S(O)_eR^{13}$, $-(C(R^9)(R^{10}))_n-CO_2R^{11}$, $-(C(R^9)(R^{10}))_n-CONR^{11}R^{12}$ or $-(C(R^9)(R^{10}))_n-COR^{11}$; more preferably, R^6 and R^8 are each hydrogen or R^8 is hydrogen and R^6 is $-(C(R^9)(R^{10}))_n-CO_2R^{11}$. R^{13} is preferably C_1-C_6 alkyl or R^{15}-phenyl. Q is preferably $-NR^{17}-$, $-O-$ or $-S(O)_e-$, with $-NR^{17}-$ being more preferred. When Q is $-NR^{17}-$, R^{17} is preferably hydrogen, C_1-C_6 alkyl or C_2-C_6 alkenyl.

E is preferably R^3-phenyl. Z^1 is preferably hydrogen, or Z^1 and Z^2 together are ethylene or propylene, and with the atoms to which they are attached form a 5- or 6-membered ring. Y^1 is preferably $-(C(R^9)(R^{10}))_m$ or $-(C(R^9)(R^{10}))_m$-G, wherein m is preferably 0 or 1. In the definition of Y^2, m is preferably 0 or 1. J is preferably $-O-$, $-N(Z^2)-$ or $-N(Z^2)C(O)-$.

Preferred are compounds wherein A^4 is a bond. Also preferred are compounds wherein A^1, A^2, A^3 and A^4 comprise an indolyl ring. Preferred compounds of formula I comprise compounds wherein A^1, A^2, A^3 and A^4 comprise an indolyl ring, R^5 and R^6 are each hydrogen and Q is $-NR^{17}-$, that is, compounds having the partial structure

Also preferred are compounds of formula I wherein R^7 and R^8 are each hydrogen, s is 2, Y^1 is $-(C(R^9)(R^{10}))_m-$ or $-(C(R^9)(R^{10}))_m$-G-, and J is $-O-$, $-N(Z^2)-$ or $-N(Z^2)C(O)-$. Another group of preferred compounds is that wherein Y^1 is $-(C(R^9)(R^{10}))_m-$ and J is $-N(Z^2)C(O)-$.

This invention also relates to the use of a compound of formula I in the treatment of asthma, cough, bronchospasm, inflammatory

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diseases such as arthritis, central nervous system conditions such as migraine and epilepsy, nociception, and various gastrointestinal disorders such as Crohn's disease.

In another aspect, the invention relates to a pharmaceutical
5   composition comprising a compound of formula I in a pharmaceutically acceptable carrier. The invention also relates to the use of said pharmaceutical composition in the treatment of asthma, cough, bronchospasm, inflammatory diseases such as arthritis, migraine, nociception, and various gastrointestinal disorders such as Crohn's
10   disease.

DETAILED DESCRIPTION

As used herein, the term "alkyl" means straight or branched alkyl chains. "Lower alkyl" refers to alkyl chains of 1-6 carbon atoms and,
15   similarly, lower alkoxy refers to alkoxy chains of 1-6 carbon atoms.

"Alkenyl" means a straight or branched alkane chain of 2-6 carbon atoms having one double bond.

"Cycloalkyl" refers to cyclic alkyl groups of 3-6 carbon atoms.

"Aryl" means phenyl, naphthyl, indenyl, tetrahydronaphthyl,
20   indanyl, anthracenyl or fluorenyl.

"Halogeno" refers to fluoro, chloro, bromo or iodo atoms.

"Heterocycloalkyl" refers to 4- to 6-membered saturated rings comprising 1 to 3 heteroatoms independently selected from the group consisting of -O-, -S- and -N(R^{16})-, with the remaining ring members being
25   carbon. Examples of heterocycloalkyl rings are tetrahydrofuranyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl and piperazinyl. R^4-heterocycloalkyl refers to such groups wherein substitutable ring carbon atoms have an R^4 substituent.

"Heteroaryl" refers to 5- to 10-membered single or
30   benzofused aromatic rings comprising 1 to 4 heteroatoms independently selected from the group consisting of -O-, -S- and -N=, provided that the rings do not include adjacent oxygen and/or sulfur atoms. Examples of single-ring heteroaryl groups are pyridyl, isoxazolyl, oxadiazolyl, furanyl, pyrrolyl, thienyl, imidazolyl, pyrazolyl, tetrazolyl, thiazolyl, thiadiazolyl,
35   pyrazinyl, pyrimidinyl, pyridazinyl and triazolyl. Examples of benzofused heteroaryl groups are indolyl, quinolinyl, thianaphthenyl and benzofurazanyl. N-oxides of nitrogen-containing heteroaryl groups are also included. All positional isomers are contemplated, e.g., 1-pyridyl, 2-

pyridyl, 3-pyridyl and 4-pyridyl. R^4-heteroaryl refers to such groups wherein substitutable ring carbon atoms have an R^4 substituent.

Those skilled in the art will appreciate that the groups comprising A^1, A^2, A^3 and A^4 are shown in the above description without a free valence, but that one of A^1, A^2, A^3 or A^4 must have a free valence to bond to the $-(C(R^5)(R^6))_r$ group, that is, one of the R^2, R^{2c}, R^{10} or R^{16} substituents on one of A^1, A^2, A^3 or A^4 is replaced by a bond to the $-(C(R^5)(R^6))_r$ group.

The proviso in the definitions of R^6 and R^8 relating to compounds wherein Q is a heteroatom is intended to allow for $-OR^{11}$, $-OC(O)R^{11}$, $-N(R^{11})COR^{12}$, $-NR^{11}R^{12}$, $-SH$ or $-S(O)_eR^{13}$ substitution on compounds wherein r and/or s is 2 or 3, as long as the carbon adjacent to Q is not substituted by those groups. The proviso that three adjacent A groups do not represent $-C(O)-O-C(O)-$, $-S(O)-O-C(O)-$ or $-S(O)-O-S(O)-$ is intended to eliminate unstable ring systems.

In the definition of Q, the group $-N^+(R^{11})(R^{17})-$ refers to quaternary amine groups.

In the above definitions, wherein R^5, R^7, R^9, R^{11}, R^{12} and R^{14} are said to be independently selected from a group of substituents, we mean that R^5, R^7, R^9, R^{11}, R^{12} and R^{14} are independently selected, but also that where an R^5, R^7, R^9, R^{11}, R^{12} or R^{14} variable occurs more than once in a molecule, those occurrences are independently selected. Similarly, R^1, R^3, R^4 and the R^2 variables can be independently selected from a group of substituents, and where more than one of those variables is present, the substitutents are independently selected; those skilled in the art will recognize that the size and nature of the substituent(s) will affect the number of substituents which can be present.

Compounds of the invention can have at least one asymmetrical carbon atom and therefore all isomers, including diastereomers, enantiomers and rotational isomers are contemplated as being part of this invention. The invention includes d and l isomers in both pure form and in admixture, including racemic mixtures. Isomers can be prepared using conventional techniques, either by reacting optically pure or optically enriched starting materials or by separating isomers of a compound of formula I.

Those skilled in the art will appreciate that for some compounds of formula I, one isomer will show greater pharmacological activity than other isomers.
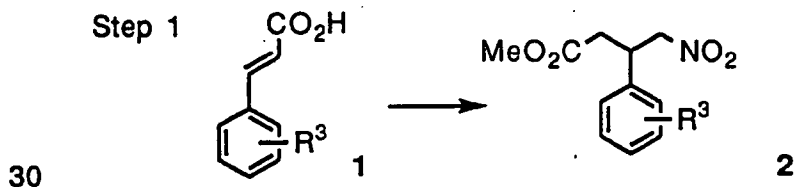
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Compounds of the invention have at least one amino group which can form pharmaceutically acceptable salts with organic and inorganic acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic,

5   malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those in the art. The salt is prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt. The free base form may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute

10   aqueous sodium bicarbonate. The free base form differs from its respective salt form somewhat in certain physical properties, such as solubility in polar solvents, but the salt is otherwise equivalent to its respective free base forms for purposes of the invention.

Certain compounds of the invention are acidic (e.g., those

15   compounds which possess a carboxyl group). These compounds form pharmaceutically acceptable salts with inorganic and organic bases. Examples of such salts are the sodium, potassium, calcium, aluminum, gold and silver salts. Also included are salts formed with pharmaceutically acceptable amines such as ammonia, alkyl amines, hydroxyalkylamines,

20   N-methylglucamine and the like.

Compounds of formula I can be prepared using methods well known to those skilled in the art. Following are typical procedures for preparing various compounds; the skilled artisan will recognize that other procedures may be applicable, and that the procedures may be suitable

25   modified to prepare other compounds within the scope of formula I.

Procedure A:

Compounds of formula I wherein $-Q-(C(R^7)(R^8))_s-$ is $-N(R^{11})CH_2CH_2-$, Z^1 is a hydrogen, Y^1 is $-CH_2-$, and J is $-N(CH_3)C(O)-$ can be prepared as shown in the following reaction scheme:
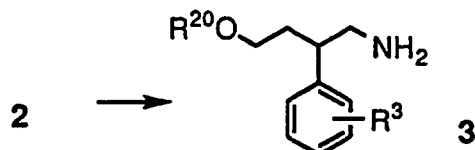
Step 1

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In step 1, a 3-(R^3-phenyl)-2-propenoic acid (1) is treated with a lower alkyl alcohol such as CH_3OH in the presence of a suitable acid catalyst such as HCl in the range of 0 to 100°C to give the corresponding ester. This ester is reacted with a nitroalkane such as CH_3NO_2 in the
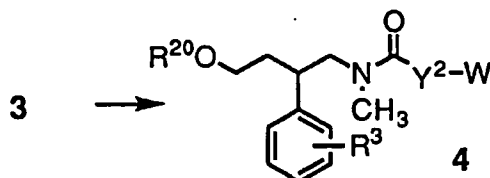
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presence of a suitable base such as benzyltrimethylammonium hydroxide
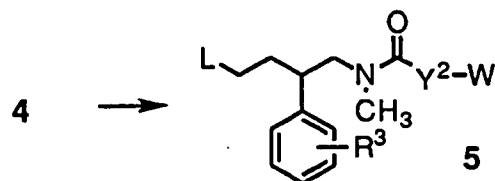at a temperature range of 0 to 100°C to give the desired compound **2**.

Step 2

$$\textbf{2} \longrightarrow \text{R}^{20}\text{O} \diagdown \diagup \diagdown \text{NH}_2 \quad \text{(}\diagdown\text{R}^3\text{)} \quad \textbf{3}$$

In step 2, compound **2** is reacted with a strong reducing
agent such as LiAlH_4 or $\text{BH}_3 \cdot \text{DMS}$ in an inert organic solvent such as
THF, ether or benzene, preferably THF, at a temperature range from 0 to
80°C. The resulting amino alcohol is reacted with an electrophile such as
a compound of formula R^{20}L^1, wherein R^{20} is a suitable hydroxyl-
protecting group such as $(\text{R}^{21})_3\text{Si-}$, wherein R^{21} are independently
selected lower alkyl groups (e.g., methyl, ethyl, isopropyl or *t*-butyl), and L^1
is a leaving group such as Cl or Br.

Step 3

$$\textbf{3} \longrightarrow \text{R}^{20}\text{O} \diagdown \diagup \diagdown \overset{\text{O}}{\underset{\underset{\text{CH}_3}{\text{N}}}{\text{N}}} \text{Y}^2\text{-W} \quad \text{(}\diagdown\text{R}^3\text{)} \quad \textbf{4}$$

In step 3, amine **3** is acylated by standard procedures, for
example by treatment with an acid chloride, WY^2COCl, in the presence of
an amine base in an inert organic solvent such as CH_2Cl_2 or toluene,
preferably CH_2Cl_2, at a temperature of from -10 to 50°C. Suitable bases
include $(\text{CH}_3)_3\text{N}$, Et_3N and pyridine, preferably Et_3N. Other coupling
methods known to those skilled in the art, such as EDC coupling, may also
be employed. The resulting amide is treated with a base such as NaH or
LDA, in an inert organic solvent such as THF, ether, DMSO or DMF,
preferably THF. The resulting anion is treated with an alkylating agent
R^{11}L, wherein R^{11} is as defined above and L is a suitable leaving group
such as Cl, Br, I, triflate or mesylate; preferably R^{11}L is CH_3I. The
reactions are typically run at 0 to 50°C.

Step 4

$$\textbf{4} \longrightarrow \text{L} \diagdown \diagup \diagdown \overset{\text{O}}{\underset{\underset{\text{CH}_3}{\text{N}}}{\text{N}}} \text{Y}^2\text{-W} \quad \text{(}\diagdown\text{R}^3\text{)} \quad \textbf{5}$$
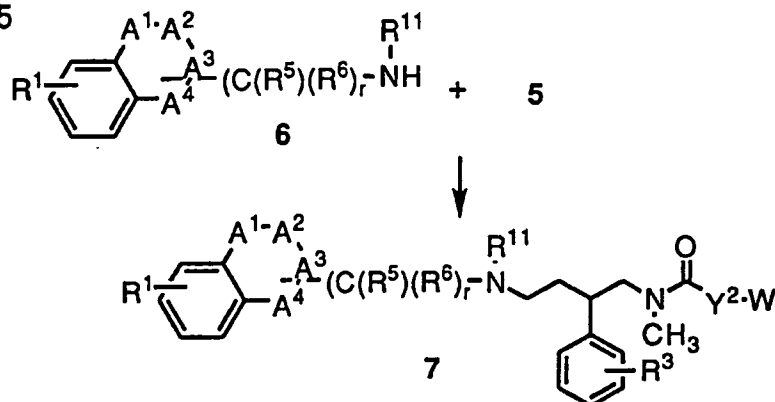
In step 4, the free hydroxyl group is regenerated by treatment
of compound **4** with a fluoride reagent such as tetrabutylammonium

- 10 -

fluoride. The hydroxyl group is converted to a suitable leaving group L, as defined above, preferably mesylate. The corresponding mesylate can be obtained by treatment with CH_3SO_2Cl in a suitable solvent such as CH_2Cl_2 in the presence of a base such as Et_3N.
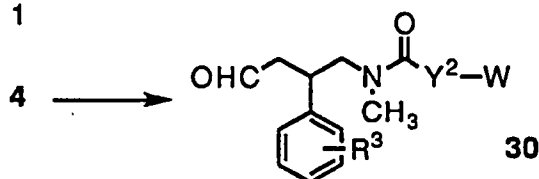
Step 5

In step 5, compound **5** is treated with compound **6** in an inert solvent such as CH_2Cl_2, THF or DMF, preferably DMF, preferably with a catalytic amount of NaI, and preferably at temperatures from 20 to 80°C.

Procedure A1:

Step 1

Alternatively to Procedure A, compound **4** is treated with a fluoride reagent such as tetrabutylammonium fluoride to regenerate the free hydroxyl group. The resulting compound is converted to aldehyde **30** by a suitable oxidation procedure, for example by the Swern procedure as described in *Tetrahedron*, 1978, **34**, 1651.
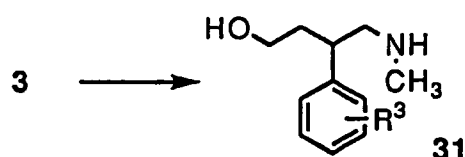
Step 2

$$6 \ + \ 30 \ \longrightarrow \ 7$$

In step 2, compound **30** is reacted with an amine of formula **6** in an alcohol such as CH_3, CH_3CH_2OH or more preferably CF_3CH_2OH, in the presence of a dehydrating agent such as molecular sieves and a reducing agent such as $NaBH_3CN$ or under hydrogenation conditions ($H_2/Pd/C$). A suitable temperature range is 0 to 60°C.

<u>Procedure A2</u>:

Step 1

3 ⟶ HO⌒⌒ⵑ NH·CH₃ / R³ **31**
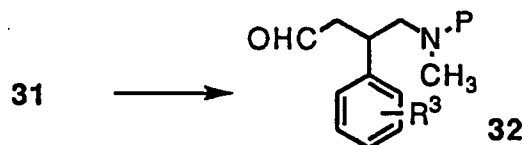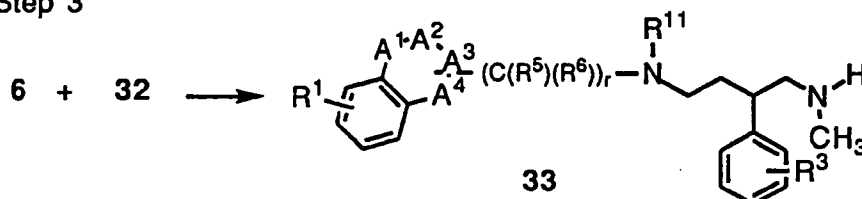
As another alternative to Procedure A, compound **3** is
converted to the formamide by standard procedures, for example by
5   treatment with ethylformate, preferably at a temperature from 30 to 60°C.
The resulting formamide is treated with a suitable reducing reagent such
as BH₃·DMS or AlH₃, preferably BH₃·DMS. The resulting amine-borane
complex and the silyl protecting group are hydrolyzed by treatment with
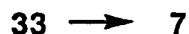aqueous acid such as HCl, preferably at a temperature from 50 to 100°C.

Step 2

31 ⟶ OHC⌒⌒ N·P / CH₃ / R³ **32**

10

In step 2, the amino group in compound **31** is suitably
protected such as by treatment with di-*t*-butyl dicarbonate to obtain the
t-butyl carbamate. The hydroxyl group is converted to the aldehyde by a
suitable oxidation procedure, for example by the Swern procedure.

Step 3

6 + 32 ⟶ R¹⌼ A¹-A² A³ -A⁴ (C(R⁵)(R⁶))ᵣ—N-R¹¹ ⌒⌒ N·H / CH₃ / R³ **33**

15

In step 3, compound **32** is reacted with an amine of formula
6 in manner such as that described in Procedure A1, Step 2. The free
methylamino group is regenerated by treatment with acid such as
trifluoroacetic acid or HCl in the presence of a suitable solvent such as
20   CH₂Cl₂ or CH₃OH.

Step 4

33 ⟶ 7

In step 4, compound **33** is acylated by standard procedures,
for example by treatment with an acid chloride, WY₂COCl, in the presence
of an amine base in an inert organic solvent such as CH₂Cl₂ or toluene,
25   preferably CH₂Cl₂, at a temperature of from -10 to 50°C Suitable bases
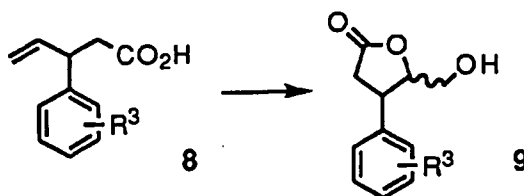include (CH₃)₃N, Et₃N and pyridine, preferably Et₃N. Other coupling

methods known to those skilled in the art, such as EDC coupling, may also be employed.

Procedure B:

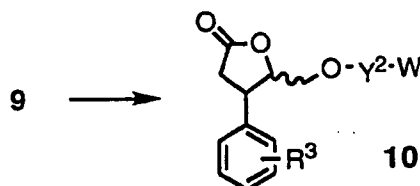Compounds of formula I wherein -Q-(C(R^7)(R^8))$_s$- is

5   -N(R^{11})CH$_2$CH$_2$-, Z^1 is hydrogen, Y^1 is -C(OH)H-, and J is -O- can be prepared as shown in the following reaction scheme:
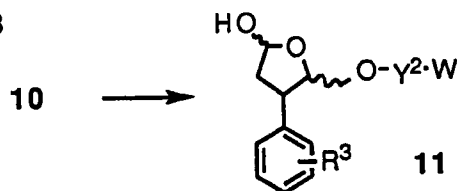
Step 1

In step 1, the 3-(R^3-phenyl)-4-pentenoic acid **8**, is reacted with an oxidizing agent such as dimethyl dioxirane or m-CPBA in an inert

10   organic solvent such as CH$_2$Cl$_2$ or toluene, preferably at reaction temperatures from 0 to 60°C. An acidic catalyst such as Amberlyst-15 or formic acid is added to give the desired lactone **9**.
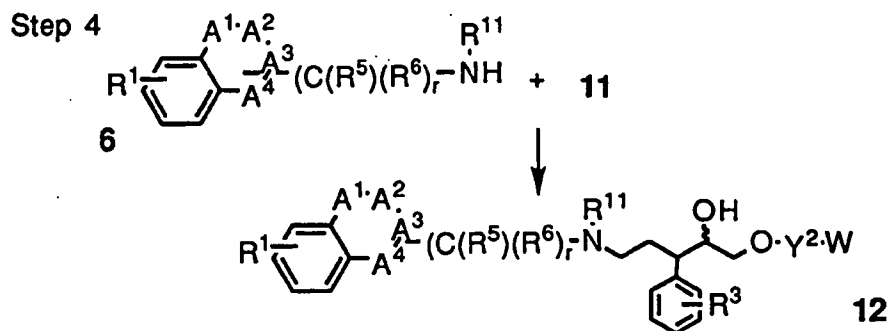
Step 2

In step 2, lactone **10** is reacted with an electrophile L^1-Y^2-W

15   wherein L^1 is a leaving group such as Cl or Br. The reaction is carried out in the presence of a silver salt such as Ag$_2$O in an organic solvent such as DMF or THF, most preferably DMF, at a temperature of 0 to about 50°C.

Step 3

In step 3, compound **10** is dissolved in an inert organic

20   solvent such as CH$_2$Cl$_2$, THF or toluene, preferably CH$_2$Cl$_2$, and treated with a reducing agent such as DIBAL-H at temperatures from about -78°C to room temperature.

- 13 -

Step 4

$$R^1 \diagdown A^1 \cdot A^2 \diagdown A^3 \diagdown A^4 - (C(R^5)(R^6))_r - \overset{R^{11}}{NH} + \quad 11$$

6

$$R^1 \diagdown A^1 \cdot A^2 \diagdown A^3 \diagdown A^4 - (C(R^5)(R^6))_r - \overset{R^{11}}{N} \diagdown \diagdown \overset{OH}{\diagdown} O \cdot Y^2 \cdot W$$
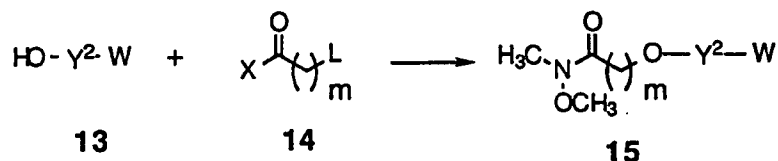$$\overset{|}{R^3}$$
12

In Step 4, compound **11** is reacted with an amine of formula
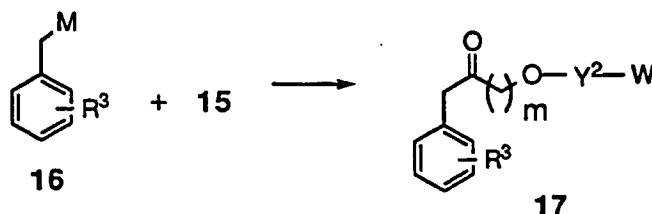**6** in a manner such as that described in Procedure A1, Step 2.

Procedure C:

5   Compounds of formula I wherein $-Q-(C(R^7)(R^8))_s-$ is
$-N(R^{11})(CH_2)_s-$ and s is 2 or 3, Z^1 is hydrogen, Y^1 is
$-C(=NO(C(R^9)(R^{10}))_rT)(CH_2)_m-$ and m is 1 to 3, and J is -O- can be
prepared as shown in the following reaction scheme:

Step 1

$$HO-Y^2-W + X \overset{O}{\underset{m}{\diagdown}} L \longrightarrow H_3C \underset{OCH_3}{\overset{O}{\diagdown}} \overset{O}{\underset{m}{\diagdown}} O-Y^2-W$$

13   14   15

10   In step 1, an alcohol with the structure **13** is treated with a
base such a NaH or LDA, preferably NaH, in an inert solvent such as THF
or DMF. The resulting alkoxide is added to an electrophile such as a
compound of formula **14** wherein m is 1, 2 or 3 and L is a leaving group
as defined above, preferably Br, and X is $-N(CH_3)OCH_3$ or -Oalkyl.

15   Preferable reaction temperatures range from -20 to 50°C. When X is
Oalkyl, it is then treated with $HN(CH_3)OCH_3$ and $Al(CH_3)_3$ in an inert
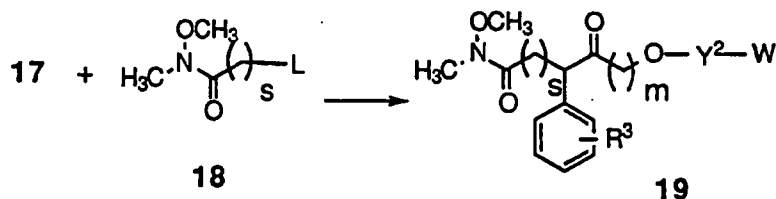organic solvent such as THF or toluene at a temperature of -20 to 40°C.

Step 2

$$\overset{M}{\diagdown}_{R^3} + \quad 15 \longrightarrow \overset{O}{\diagdown} \overset{O}{\underset{m}{\diagdown}} O-Y^2-W$$
$$\overset{|}{R^3}$$

16   17

In step 2, compound **15** is treated with a reagent of formula
20   **16** wherein M is Li, MgCl or MgBr, in an inert organic solvent such as THF
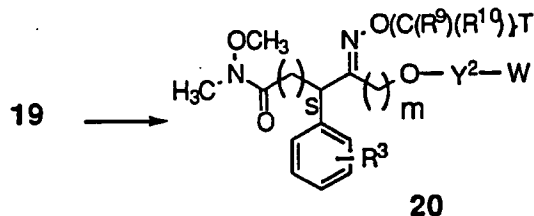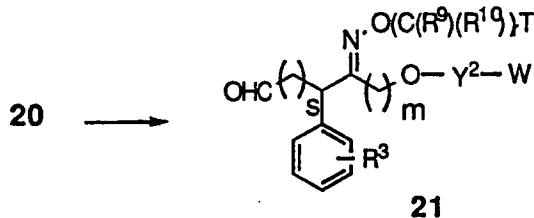or ether, at a temperature of -78 to 40°C.

Step 3

17 + H₃C·N⧸OCH₃⧹⧸( )⧹ₛ—L
           ‖
           O
        18

→

H₃C·N⧸OCH₃⧹⧸( )⧹ₛ⧸⧹⧸( )⧹ₘ—O—Y²—W
   ‖   ‖
   O   O
              ⬡—R³
           19

In step 3, compound **17** is treated with a suitable base such as NaN(TMS)$_2$ or LDA, preferably NaN(TMS)$_2$, in an inert organic solvent such as THF. The resulting anion is treated with a compound of formula

5   **18** wherein s is 1 or 2 and L is a leaving group as defined above, in an inert organic solvent such as THF or ether at reaction temperatures ranging from -78 to 30°C.

Step 4

19 →

H₃C·N⧸OCH₃⧹⧸( )⧹ₛ⧸⧹⧸N·O(C(R⁹)(R¹⁰))$_r$T
   ‖   ‖
   O   ⧸( )⧹ₘ—O—Y²—W
              ⬡—R³
           20

A compound of formula **19** is converted to the corresponding

10 oxime of formula **20** by treating the ketone **19** with a hydroxylamine derivative of the formula H$_2$NO(C(R⁹)(R¹⁰))$_r$T, in a suitable organic solvent such as pyridine at a temperature of from 25 to 100°C. Alternatively, a low molecular weight alcohol (e.g. CH$_3$OH or CH$_3$CH$_2$OH) can be used as the solvent, in which case a base such as sodium acetate must be added.

Step 5

20 →

OHC⧸( )⧹ₛ⧸⧹⧸N·O(C(R⁹)(R¹⁰))$_r$T
                ‖
                ⧸( )⧹ₘ—O—Y²—W
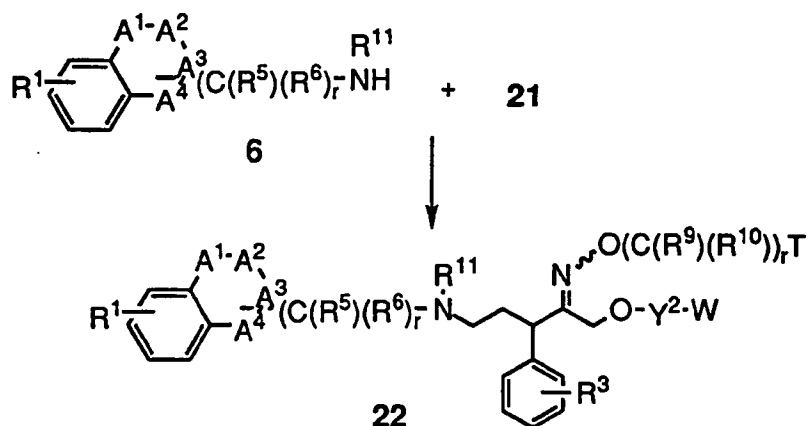   ⬡—R³
      21

15

In step 5, compound **20** is treated with a reducing agent such as DIBAL-H in an inert organic solvent such as THF or CH$_2$Cl$_2$ at a temperature from -78 to -40°C.
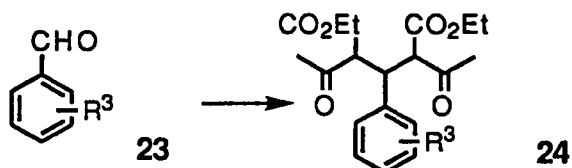
Step 6

In Step 6, compound **21** is reacted with an amine of formula **6** in a manner such as that described i Procedure A1, Step 2.
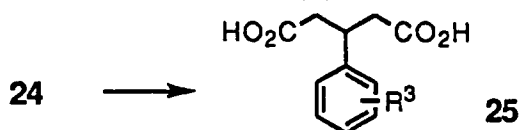
<u>Procedure D</u>:

Compounds of formula I wherein -Q-$(C(R^7)(R^8))_s$- is -$N(R^{11})CH_2CH_2$-, Z^1 is hydrogen, Y^1 is -$CH_2C(O)$-, and J is -$N(CH_3)$- can be prepared as shown in the following reaction scheme:

Step 1
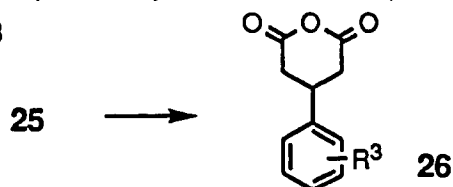

In step 1, an aldehyde of formula **23** is reacted with ethylacetoacetate in polar organic solvent such as CH_3CH_2OH in the presence a suitable base, e.g., piperidine, at a temperature of 10 to 50 °C.

Step 2

In step 2, compound **24** is converted to the diacid compound of formula **25** by treatment with a strong base such as NaOH in an aqueous alcoholic solvent such as CH_3CH_2OH at a temperature from 60 to 100°C, preferably at the reflux temperature of the solvent.
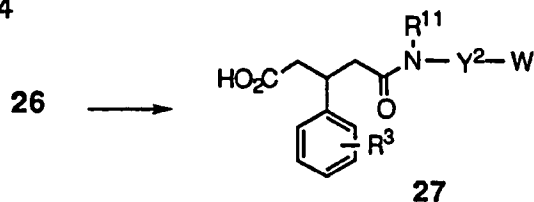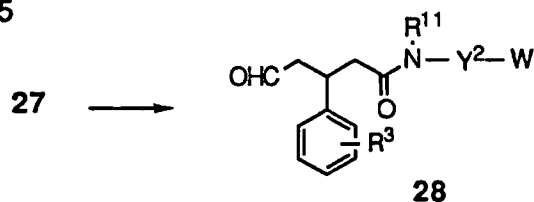
Step 3

In step 3, compound 25 is treated with a dehydrating reagent such as CH_3COCl or DCC, preferably CH_3COCl.
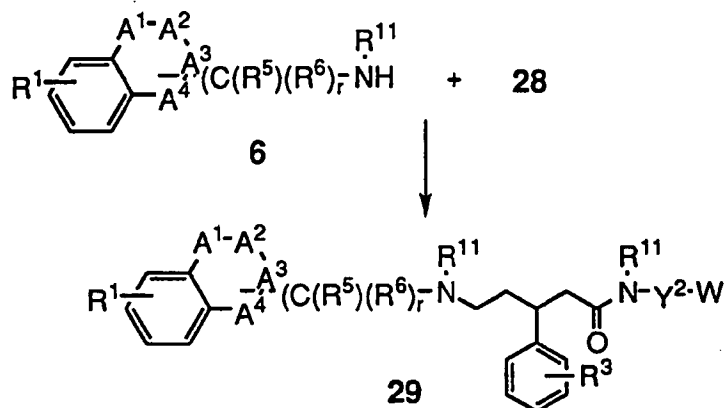
Step 4

26   ⟶

$$HO_2C \cdots \overset{R^{11}}{\underset{O}{N}} - Y^2 - W$$

27

Treatment of anhydride 26 with an amine of the formula W-
5 Y^2-NHR^{11} in a suitable solvent such as CH_2Cl_2 in the presence of a suitable base such as Et_3N or N,N-dimethylamino-pyridine gives acid 27.

Step 5

27   ⟶

$$OHC \cdots \overset{R^{11}}{\underset{O}{N}} - Y^2 - W$$

28

Acid 27 is converted to the alcohol by a suitable reduction procedure. For example, a compound 27 a treated with 1,1'-carbonyl-
10 diimidazole in an organic solvent such as ethyl acetate in the presence of a suitable base such as N,N-dimethylaminopyridine followed by treatment with aqueous $NaBH_4$. The alcohol is converted to the aldehyde 28 by a suitable oxidation procedure.

Step 6

$$R^1 \cdots \overset{A^1-A^2}{\underset{A^4}{A^3}}(C(R^5)(R^6))_r - \overset{R^{11}}{N}H \quad + \quad 28$$

6

↓

$$R^1 \cdots \overset{A^1-A^2}{\underset{A^4}{A^3}}(C(R^5)(R^6))_r - \overset{R^{11}}{N} \quad \overset{R^{11}}{N} - Y^2 - W$$

29
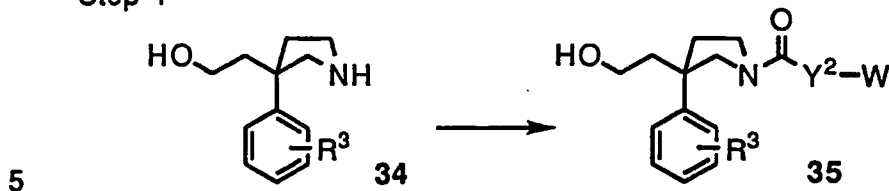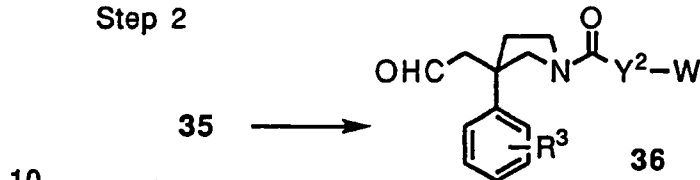
15   In Step 6, compound 28 is reacted with an amine of formula 6 in a manner such as that described in Procedure A1, Step 2.
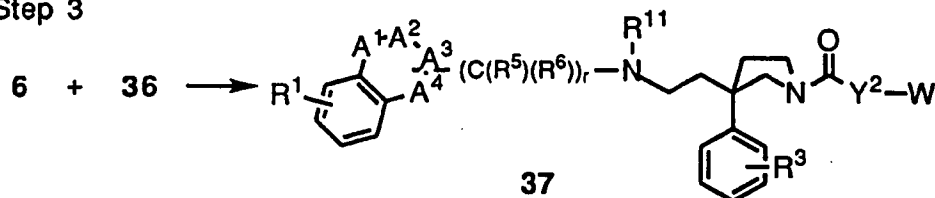
Procedure E:

Compounds of formula I wherein $-Q-(C(R^7)(R^8))_s-$ is $-N(R^{11})CH_2CH_2-$, Y^1 is $-CH_2-$, J is $-N(Z^2)CO-$ and Z^1 and Z^2 together are $-CH_2CH_2-$ can be prepared as shown in the following reaction scheme:

Step 1

In step 1, 3-(R^3-phenyl)-3-(2-hydroxyethyl)-pyrrolidine **34** (which can be obtained by the procedure described in T.B. Burkholder et al. *Bioorg. & Med. Chem. Let. 6*, (1996), p. 951) is acylated by standard procedures as described in Procedure A2, Step 4.

Step 2

35 $\longrightarrow$

In step 2, compound **35** is converted to aldehyde **36** by a suitable oxidation procedure, for example by the Swern procedure.

Step 3

6 + **36** $\longrightarrow$
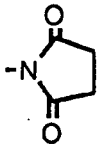
In step 3, compound **36** is reacted with an amine of formula 6 in a procedure such as described in Procedure A1, Step 2.

Reactive groups not involved in the above processes can be protected during the reactions with conventional protecting groups which can be removed by standard procedures after the reaction. The following Table 1 shows some typical protecting groups:

Table 1

Group to be Protected	Group to be Protected and Protecting Group
—COOH	—COOalkyl, —COObenzyl, —COOphenyl
$>$NH	$>$NCOalkyl, $>$NCObenzyl, $>$NCOphenyl,
	$>$NCH$_2$OCH$_2$CH$_2$Si(CH$_3$)$_3$ $>$NC(O)OC(CH$_3$)$_3$,
	$>$N-benzyl, $>$NSi(CH$_3$)$_3$, $>$NSi-C(CH)$_3$ with CH$_3$ substituents
—NH$_2$	-N-succinimido ring (with two C=O groups and O, O)
—OH	—OCH$_3$, —OCH$_2$OCH$_3$, —OSi(CH$_3$)$_3$, —OSi-C(CH)$_3$ with CH$_3$ substituents
	or —OCH$_2$phenyl

Compounds of formula I have been found to be antagonists
of NK$_1$ and/or NK$_2$ and/or NK$_3$ receptors, and are therefore useful in
5   treating conditions caused or aggravated by the activity of said receptors.

The present invention also relates to a pharmaceutical
composition comprising a compound of formula I and a pharmaceutically
acceptable carrier. Compounds of this invention can be administered in
conventional oral dosage forms such as capsules, tablets, powders,
10   cachets, suspensions or solutions, or in injectable dosage forms such as
solutions, suspensions, or powders for reconstitution The pharmaceutical
compositions can be prepared with conventional excipients and additives,
using well known pharmaceutical formulation techniques.
Pharmaceutically acceptable excipients and additives include non-toxic
15   and chemically compatibile fillers, binders, disintegrants, buffers,
preservatives, anti-oxidants, lubricants, flavorings, thickeners, coloring
agents, emulsifiers and the like.

The daily dose of a compound of formula I for treating
asthma, cough, bronchspasm, inflammatory diseases, migraine,
20   nociception and gastrointestinal disorders is about 0.1 mg to about 20
mg/kg of body weight per day, preferably about 0.5 to about 15 mg/kg. For
an average body weight of 70 kg, the dosage range is therefore from
about 1 to about 1500 mg of drug per day, preferably about 50 to about

- 19 -

200 mg, more preferably about 50 to about 500 mg/kg per day, given in a single dose or 2-4 divided doses. The exact dose, however, is determined by the attending clinician and is dependent on the potency of the compound administered, the age, weight, condition and response of the patient.

Following are examples of preparing starting materials and compounds of formula I.

Example 1
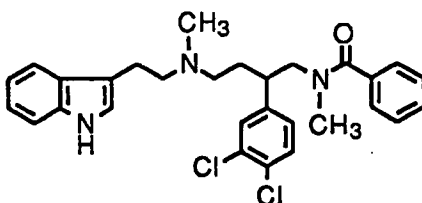
Step 1:   Reflux a solution of 3-(3,4-dichlorophenyl)-2-propenoic acid (26.02 g, 0.12 mol), CH_3OH (500 mL) and saturated methanolic HCl (5.0 mL) for 14 h. Cool to precipitate white crystals and collect by filtration to give 22.6 g of the methyl ester product (0.098 mol, 82%). Concentrate the filtrate and purify on a short silica gel column, eluting with 3:1 hexane: EtOAc to obtain an additional 4.43 g of the methyl ester (0.019 mol, 16%).

Step 2:   Treat the product of Step 1 (25.0 g, 0.108 mol) with 40% methanolic benzyltrimethylammonium hydroxide (9.3 mL, 22 mmol) and CH_3NO_2 (210 mL) and heat at 80°C for 1.5 h. Dilute the reaction mixture with diethyl ether (Et_2O) (1 L), wash with 1N HCl (400 mL and 100 mL) and brine (500 mL), dry with $MgSO_4$ and concentrate. Chromatograph on silica gel, eluting with 3:1 hexane:EtOAc, to obtain 31.0 g of methyl 3-(3,4-dichlorophenyl)-4-nitrobutyrate (0.106 mol, 98%).

Step 3:   To a 1M Et_2O solution of $LiAlH_4$ (200 mL, 200 mmol) at 0°C, slowly add the product of Step 2 (14.35 g, 49.1 mmol) dissolved in tetrahydrofuran (THF) (100 mL). Allow the reaction mixture to warm to room temperature and stir for 45 min. After recooling to 0°C, quench the excess $LiAlH_4$ by the careful addition of aqueous saturated Na_2SO_4 (20 mL). Dry the solution with Na_2SO_4 and filter. Wash the lithium salts with Et_2O (3 x 300 mL). Concentrate the combined filtrates to give 8.65 g of 4-amino-3-(3,4-dichlorophenyl)-butanol as a white solid (36.9 mmol, 75%).

Step 4:   Treat a solution of the amino alcohol from Step 3 (8.13 g, 34.7 mmol) and imidazole (3.56 g, 52.3 mmol) in CH_2Cl_2 (350 mL) with

. *tert*-butyldimethylsilyl chloride (7.84 g, 52.0 mmol). After stirring for 1 h, wash the reaction with 0.1 N HCl (350 mL) and extract the aqueous layer with CH_2Cl_2 (100 mL). Wash the combined organic layers with saturated $NaHCO_3$ (200 mL) and brine (200 mL), dry with K_2CO_3, and concentrate

5   to give 11.4 g of the silylated product as a pale yellow viscous liquid (34.2 mmol, 98 %).

Step 5:   Treat the amine from step 4 (15.3 g, 44 mmol) in CH_2Cl_2 (250 mL) with triethyl amine (Et_3N) (13 mL, 93 mmol) and benzoyl chloride (8.0 mL, 69 mmol). Stir at room temperature for 1.5 h, then wash the

10   reaction mixture with H_2O (500 mL) and extract the aqueous layer with CH_2Cl_2 (2 x 100 mL). Wash the combined organic layers with 0.3 N HCl (150 mL), saturated $NaHCO_3$ (150 mL) and brine (200 mL), dry with $MgSO_4$ and concentrate. Chromatograph the crude material on silica gel, eluting with 6:1 to 3:1 hexane:EtOAc to give 13.7 g of the benzamide (30

15   mmol, 69%).

Step 6:   Treat the product of step 5 (10.54 g, 23.3 mmol) in THF (170 mL) with 60 % NaH (1.87 g, 47 mmol) followed by CH_3I (1.9 mL, 30.5 mmol). Heat the reaction mixture at 60°C for 30 min and then partition between Et_2O (250 mL) and H_2O (500 mL). Extract the aqueous layer

20   with Et_2O (500 mL), wash the combined organic layers with brine (250 mL), dry with $MgSO_4$ and concentrate to give 9.9 g of the methyl benzamide product as a colorless oil (21 mmol, 91%).

Step 7:   Treat the product of Step 6 (9.9 g, 21 mmol) in THF (125 mL) with a 1 M THF solution of t-butylammonium fluoride (50 mL, 50 mmol)

25   and stir for 4 h. Partition the reaction mixture between H_2O (200 mL) and Et_2O (100 mL). Extract the aqueous layer with Et_2O (2 x 100 mL), combine the organic layers and wash with brine (100 mL), dry with $MgSO_4$ and concentrate. Purify the crude product by recrystalization in CH_2Cl_2:hexane to give 5.5 g of the alcohol product as white crystals (15.6

30   mmol, 74.4 %).

Step 8:   Stir the product of step 7 (1.37 g, 3.8 mmol) in CH_2Cl_2 (20 mL) with Et_3N (0.6 mL, 4.3 mmol) and C H_3SO_2Cl (0.32 mL, 4.1 mmol) for 45 min, then add the reaction mixture to 0.3 N HCl (200 mL) and extract with CH_2Cl_2 (3 x 100 mL). Wash the combined organic layers with

35   saturated $NaHCO_3$ (100 mL) and brine (100 mL), dry with $MgSO_4$ and concentrate to obtain 1.49 g of the methanesulfonate ester as a colorless viscous oil (3.47 mmol, 89%).

Step 9: Heat the product of step 8 (0.499 g, 1.16 mmol) in DMF (5 mL) with Nω-methyl tryptamine (0.241 g, 1.38 mmol) and NaI (16.4 mg, 0.11 mmol) at 50°C for 38 h. Add the reaction mixture to saturated NaHCO$_3$ (100 mL) and extract with CH$_2$Cl$_2$ (3 x 40 mL), wash the combined organic layers with brine (80 mL), dry with MgSO$_4$ and concentrate. Chromatograph on silica gel, eluting with 20:1:0.1 to 13:1:0.1 CH$_2$Cl$_2$:MeOH:NH$_3$ (aq.), gave 413 mg of the title compound as a white foam (0.81 mmol, 70 %). HRMS (FAB, M+H+): m/e calc'd for [C$_{29}$H$_{32}$Cl$_2$N$_3$O]+ 508.1922; found 508.1929.
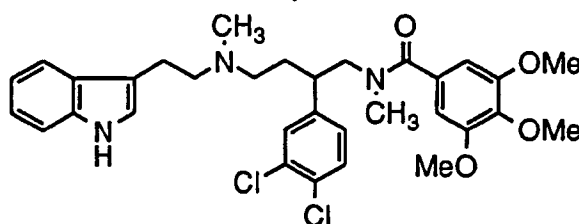
Example 2

Step 1: To a 0°C solution of the product of Example 1, Step 4 (8.0 g, 22.9 mmol) in DMF, add 4-methylmorpholine (NMM) (2.5 mL, 22.9 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (6.5 g, 34.4 mmol), 1-hydroxybenzotriazole hydrate (HOBT) (3.0 g, 22.9 mmol) and 3,4,5-trimethoxybenzoic acid (4.9 g, 22.9 mmol). Stir the reaction mixture at 0°C for 30 min., then at room temperature overnight. Concentrate under high vacuum and resuspend the resulting material in H$_2$O and extract with EtOAc. Wash the combined organic layers with saturated NaHCO$_3$, dry with MgSO$_4$ and concentrate. Chromatograph the crude product on silica gel, eluting with 20:1 CH$_2$Cl$_2$:NH$_3$ saturated CH$_3$OH to give 9.0 g of amide as a light yellow solid (72 %).

Steps 2-5: Convert the product of Step 1 to the title compound using procedures similar to those described in Example 1, Steps 6 to 9. MS (FAB, M+H+): m/e 598; Analysis for C$_{32}$H$_{37}$Cl$_2$N$_3$O$_4$: Calc'd C, 64.21; H, 6.23; N, 7.20%; Found: C, 63.84; H, 6.37; N, 7.00.
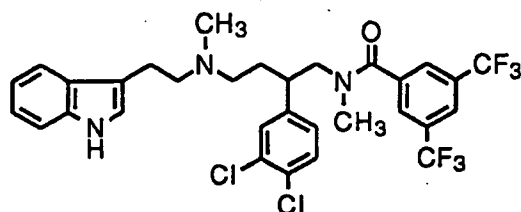
Example 2a
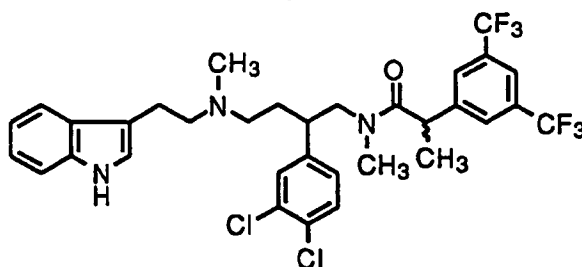
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Using the procedure of Example 2, substitute 3,5-bis(trifluoro-methyl)phenylacetic acid for 3,4,5-trimethoxybenzoic acid in step 1, and in step 2, methylate the benzylic position of the phenyl acetyl group and the amide position to obtain the title compound. MS (FAB, M+H+): m/e 672.

5

Example 2b
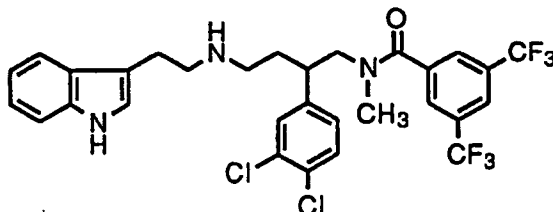
Using the procedure of Example 2, substitute 3,5-bis(trifluoro-methyl)benzoic acid for 3,4,5-trimethoxybenzoic acid in step 1, and tryptamine for Nω-methyltryptamine in step 5 to obtain the title compound.

10   HRMS (FAB, M+H+): m/e calc'd for $[C_{30}H_{28}N_3OCl_2F_6]^+$ 630.1514; found 630.1513.

Example 2c

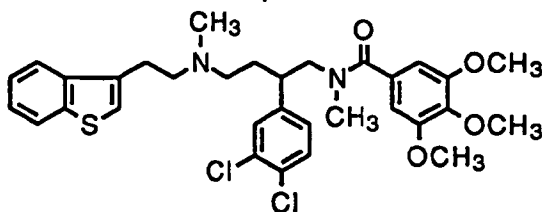Using the procedure of Example 2, substitute 3,5-bis(trifluoro-

15   methyl)benzoic acid for 3,4,5-trimethoxybenzoic acid in step 1 to obtain the title compound.

Example 2d
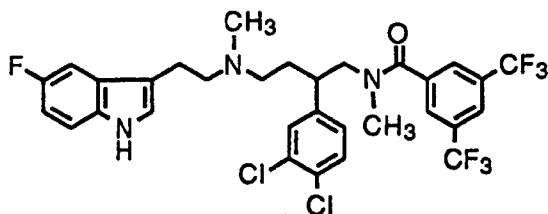
Using the procedure of Example 2c, substitute 5-fluoro-Nω-methyl-

20   tryptamine for Nω-methyltryptamine in step 5 to obtain the title compound. HRMS (FAB, M+H+): m/e calc'd for $[C_{31}H_{29}N_3OCl_2F_7]^+$ 662.1576; found 662.1584.

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Example 2e

Using the procedure of Example 2, substitute N-methyl-3-(2-amino-ethyl)benzothiophene for Nω-methyltryptamine in step 5 to obtain the title compound. HRMS (FAB, M+H+): m/e calc'd for $[C_{32}H_{37}N_2O_4Cl_2S]^+$ 615.1851; found 615.1850.

Example 3
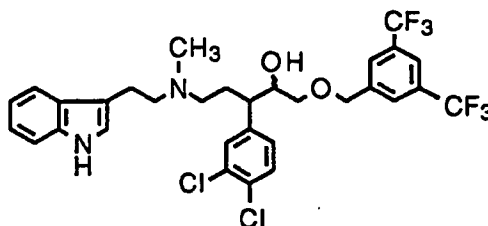
Step 1:   Cool a solution of 3-(3,4-dichlorophenyl)-2-propeneoic acid (100 g, 461 mmol) in dry DMF (500 mL) to 0 °C and treat with Cs_2CO_3 (100 g, 307 mmol). Stir the resulting off-white slurry for 15 min., then add CH_3I (33 mL, 530 mmol) via syringe. After 1 h, add additional DMF (250 mL) and stir the slurry for 14 h, then partition between ethyl acetate (EtOAc) (1.5 L) and half saturated aqueous $NaHCO_3$ (500 mL). Separate the organic layer and extract the aqueous layer with EtOAc (1 L, 500 mL). Wash the combined organic layers with half saturated aqueous $NaHCO_3$ (500 mL) and water (5 x 500 mL), then dry over Na_2SO_4 and concentrate to obtain methyl 3-(3,4-dichlorophenyl)-2-propenoate, 105.4 g (456 mmol, 99%), as light brown needles.

Step 2:   Treat a solution of the product of Step 1 (15 g, 65 mmol) in dry THF (250 mL) (kept cool in a large ambient temperature water bath) with DIBAL-H (140 mL, 140 mmol) over 30 min. Stir the resulting solution for 30 min at 23 °C, pour into Et_2O (500 mL) and treat with water (5 mL), 15 % NaOH (5 mL) and water (15 mL). Stir for 5 min, dilute the mixture with Et_2O (200 mL), add 15 % NaOH (15 mL), then add $MgSO_4$ to obtain a colorless precipitate. Remove the aluminum salts by filtration through a coarse glass frit, wash the solids with Et_2O (1 L) and concentrate the filtrate *in vacuo* to give 3-(3,4-dichloro-phenyl)-2-propene-1-ol as an off-white solid, 13.2 g (65 mmol, 99%).

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<u>Step 3:</u>   Combine a solution of the product of Step 2 (13.2 g, 65 mmol) in CH_2Cl_2 (250 mL) at 0°C with pyridine (7.89 mL, 97.5 mmol) and dimethylaminopyridine (DMAP) (397 mg, 3.25 mmol), followed by acetyl chloride (6.48 mL, 74.7 mmol). Allow the mixture to warm to 23 °C, pour

5   into 1 M HCl (100 mL) and wash the resulting organic layer with 1 M HCl (100 mL) followed by water (5 x 100 mL; pH=6.5-7). Dry the organic layer over Na_2SO_4 and concentrate, providing 3-(3,4-dichloro-phenyl)-2-propene-1-ol acetate as a colorless oil, 15.4 g (62.9 mmol, 97%).

<u>Step 4:</u>   Treat a solution of the product of Step 3 (15 g, 61 mmol,

10   dried by azeotropic distillation with toluene, 1 x 50 mL) in dry THF (250 mL) at -78°C with chlorotriethylsilane (20.2 mL, 120 mmol), rapidly followed by the addition of 0.5 M toluene solution of potassium bis(trimethylsilyl)amide (183 mL, 91.5 mmol) via addition funnel over 50 min. Allow the mixture to warm to 23 °C, then heat to reflux for 3 h. Allow the

15   solution to gradually cool overnight, then quench with saturated NH_4Cl (150 mL). Stir the resulting mixture vigorously for 3h, treat with 1M HCl (150 mL) and extract with Et_2O (500 mL). Extract the aqueous layer with Et_2O (400 mL) and wash the combined organic layers with 300 mL of 5% NaOH followed by 8 x 150 mL of 5 % NaOH. Cool the combined aqueous

20   layers to 5 °C and carefully (temperature kept to 5-10 °C) acidify with conc. HCl (ca 175 mL) to pH 1. Extract the aqueous layer with CH_2Cl_2 (2 x 800 mL), dry (Na_2SO_4) and concentrate to give 3-(3,4-di-chlorophenyl)-4-pentenoic acid as a faint yellow oil, 13.4 g (54.5 mmol, 89%).

<u>Step 5:</u>   Treat a solution of the product of Step 4 (5.0 g, 20.4 mmol) in

25   dry CH_2Cl_2 (60 mL) with purified m-CPBA (7 g, 40 mmol) [wash 13 g of commercial 55% mCPBA in 250 mL of benzene with pH 7.4 buffer (5 x 30 mL), dry (Na_2SO_4) and concentrate to give about 9 g of pure m-CPBA]. After stirring for 48 h, add Amberlyst 15 (1.2 g) and stir the mixture for 8 h. Remove the Amberlyst by filtration through a medium porosity glass frit,

30   rinsing with EtOAc. Wash the filtrate with 100 mL of saturated Na_2SO_3 / $NaHCO_3$ (1:1), dry the resulting organic layer and concentrate *in vacuo*. Take up the crude product in hexane:CH_2Cl_2 (1:1) and filter to give 3.3 g (12.6 mmol, 62%) of a mixture of isomers (3:2, *trans / cis*) of the title compound as a colorless soft solid. Concentrate the filtrate to give 2.0 g of

35   a viscous oil which is purified by silica gel chromatography (column: 7 x 15 cm; solvent: hexane:EtOAc, 5:4 gradient to 1:1) to give 1.07 g (4.1 mmol, 20%) of the pure *cis* isomer of the title compound as an oil, total yield 4.3 g (16.47 mmol, 81%).

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Step 6:   Treat a solution of 4-(3,4-dichlorophenyl)-dihydro-5-
(hydroxymethyl) 2(3H)-furanone (3.3 g, 12.6 mmol, 3:2 ratio of stereo-
isomers by NMR) in dry DMF(10 mL) with 3,5-bistrifluoromethylbenzyl
bromide (5.9 mL, 32.2 mmol) followed by Ag_2O (5.8 g, 25.3 mmol); wrap
5   the vessel in foil and stir for 2.5 d. Apply the crude material to a pad of
silica gel (10 cm x 4 cm) packed with hexane:EtOAc (1:1), washing the
pad with the same solvent until no further product is eluted as shown by
TLC; concentrate the resulting filtrate *in vacuo* to give the crude product
as a solid (10g). Dissolve the crude was dissolved in hexane:EtOAc (4:1)
10   and purify by silica gel chromatography (column: 7.5 x 19; solvent:
hexane:EtOAc, 4:1) to give 3.33 g (6.8 mmol, 54%) of isomer (*trans*)-[[[(3,5-
bis(trifluoromethyl)phenyl]methoxy]methyl]-4-(3,4-dichlorophenyl)-
dihydro-2(3H)-furanone and 1.08 g (2.2 mmol, 17%) of the corresponding
cis isomer for a total yield of 71%.
15   *Trans* isomer: HRMS (FAB, M+H+): *m/e* calc'd for $[C_{20}H_{15}O_3Cl_2F_6]^+$:
487.0302, found 487.0312.
Cis isomer: HRMS (FAB, M+H+): *m/e* calc'd for $[C_{20}H_{15}Cl_2F_6O_3]^+$:
487.0302, found 487.0297.
Step 7:   Cool a solution of the cis isomer of Step 6 (2.1g, 4.31 mmol)
20   in dry CH_2Cl_2 (50 mL) to -78 °C and treat with DIBAL-H (5.1 mL, 5.1 mmol;
1M in CH_2Cl_2). Stir for 2 h at -78 °C, then treat the solution with NaF (905
mg 22 mmol) and water (400 µL, 22 mmol, 5 eq). Allow the suspension to
warm to 23 °C and stir for 45 min., dilute the mixture with ET_2O (50 mL)
and filter through a pad of silica gel (6.5 cm x 2 cm; 150 mL vacuum glass
25   frit) packed with hexane:EtOAc (1:1)), washing the pad with hexane:EtOAc
(1:1) until no further product is evident as shown by TLC. Concentrate the
filtrate to give 1.92 g (3.86 mmol, 91%) of the title compound as a foam
which was used without further purification in the next step.
Step 8:   Stir a suspension of the lactol of Step 7 (1.03 g, 2.1 mmol),
30   Nω-methyl tryptamine (0.73 g, 4.2 mmol) and 3A molecular sieves (1.7 g)
in CF_3CH_2OH (5.0 mL) for 1 h, add $NaCNBH_3$ (0.26 g, 4.2 mmol) and stir
the reaction mixture over the weekend, then concentrate. Chromatograph
the residue on silica gel, eluting with 20:1 CH_2Cl_2/CH_3OH (saturated with
ammonia) to give 0.809 g of the desired compound as a white solid (60
35   %). MS (FAB, M+H+): *m/e* 647.

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Example 4
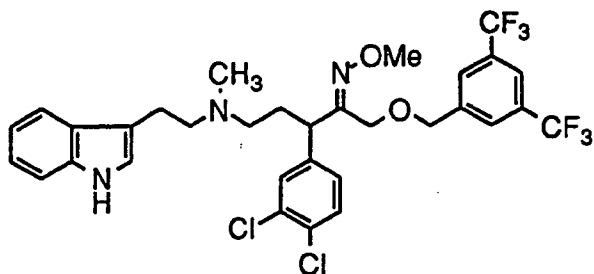
<u>Step 1:</u>   Combine 3,5-bis(triflouromethyl)benzyl alcohol (25.0 g,
0.103 mol) in THF (50 mL) with 60% NaH (4.14 g, 0.104 mol) and stir for
5   30 min. Transfer the resulting alkoxide mixture via cannula over 30 min to
a solution of methylbromoacetate (11.8 mL, 0.125 mol) in THF (250 mL).
Stir the reaction mixture for 18h and add to 0.3 N HCl (300 mL). Separate
the organic layer and extract the aqueous layer with EtOAc (2 x 150 mL).
Wash the combined organic layers with brine (200 mL), dry with MgSO4
10   and concentrate. Chromatograph on silica gel, eluting with 10:1 hexane:
EtOAc, to give the desired product as a colorless liquid (26.1 g, 80%).

<u>Step 2:</u>   Combine a suspension of N,O-dimethylhydroxylamine
hydrochloride (19.5 g, 0.20 mol) in THF (350 mL) at 0°C with AlMe3 (100
mL, 0.20 mol, 2M in toluene) and allow to warm to room temperature for
15   30 min. Cool this mixture to 0°C, add the product of Step 1 (26.1 g, 82.7
mmol) dissolved in THF (140 mL) over 30 min., warm the mixture to room
temperature and stir for 40 min. Cool the reaction mixture to 0°C, quench
by the careful addition of 1N HCl (100 mL) and concentrate. Partition the
residue between H2O (250 mL) and CH2Cl2 (300 mL), extract the
20   aqueous layer with CH2Cl2 (2 x 150 mL) dry the combined organic layers
with MgSO4 and concentrate. Chromatograph on silica gel, eluting with
3:1 hexane:EtOAc to give the product as a colorless liquid (28.1 g, 98%).

<u>Step 3:</u>   Treat a suspension of Mg (1.35 g, 55.6 mmol) in Et2O (10
mL) maintained at 30°C with a solution of α,3,4-trichlorotoluene (7.7 mL,
25   55.6 mmol) in Et2O (45 mL) over 1h and then stir for 30 min. Transfer the
resulting solution via cannula over 30 min to a -78°C solution of the
product of Step 2 (9.56 g, 27.7 mmol) in Et2O (350 mL) and warm the
reaction mixture to room temperature over 1 h. Cool the reaction mixture
to 0°C and treat with HCl saturated CH3OH (4 mL) and CH3OH (100 mL),
30   stir for 1 h and concentrate. Partition the residue between CH2Cl2 (300

mL), Et$_2$O (500 mL) and H$_2$O (250 mL), dry the organic layer with MgSO$_4$ and concentrate. Chromatograph on silica gel, eluting with 2:1 CH$_2$Cl$_2$: hexane, to give the product as a white solid (6.22 g, 50%).

Step 4: To a solution of sodium bis(trimethylsilyl)amide (2.5 mmol) in THF (20 mL) at -78°C, add, dropwise, a solution of the product from Step 3 (1.11 g, 2.5 mmol) in THF (5 mL) over 15 min. Stir at -78°C for 2 h and then add a solution of 2-bromo-N-methoxy-N-methylacetamide (455 mg, 2.5 mmol) in THF (5 mL) dropwise over 10 min. Allow the mixture to warm to room temperature over 1 h, then stir at room temperature for an additional 30 min. Add brine to the reaction mixture (2 mL) and concentrate. Partition the residue between CH$_2$Cl$_2$ (60 mL), Et$_2$O (90 mL) and H$_2$O (30 mL). Wash the organic layer with brine (30 mL), dry with Na$_2$SO$_4$ and concentrate. Chromatograph on silica gel, eluting with CH$_2$Cl$_2$ to give the product as a colorless oil (800 mg, 56%).

Step 5: Heat a mixture of the product of Step 4 (597 mg, 1.1 mmol), pyridine (10 mL) and methoxylamine hydrochloride (101.5 mg, 1.2 mmol) at 60°C for 1 h and then concentrate. Chromatogra[ph on silica gel, eluting with 3:1 hexane:EtOAc to obtain the oxime (syn-isomer) as a colorless oil (442 mg, 70%). HRMS (FAB, M+H+): *m/e* calc'd for [C$_{23}$H$_{22}$Cl$_2$F$_6$N$_2$O$_4$]+: 575.0939, found 575.0932.

Step 6: Treat the product of Step 5 (347 mg, 0.60 mmol) in THF (6 mL) at -78°C with DIBAL-H (1.8 mL, 1.8 mmol, 1M in hexane) over 15 min. Add H$_2$O (5 mL) and warm to room temperature; to this mixture, add NAF (0.2 g, 4.8 mmol) and stir for 20 min. Partition the reaction mixture between brine (25 mL) and Et$_2$O (25 mL), dry the organic layer with MgSO$_4$ and concentrate to give the crude product (298 mg, 94%).

Step 7: Treat the aldehyde of Step 6 (35 mg, 68 μmol) with Nω-methyl tryptamine (26.2 mg, 0.15 mmol), CF$_3$CH$_2$OH (0.4 mL) and crushed 3Å molecular sieves (36 mg) and stir for 20 min. Add NaCNBH$_3$ (13 mg, 0.21 mol), stir for 14 h and concentrate. Chromatograph on silica gel, eluting with 10:1:0.1 CH$_2$Cl$_2$:MeOH:NH$_3$(aq) to give the title compound as a colorless oil (32 mg, 70%). MS (FAB, M+H+): *m/e* calc'd 674.1776; found 674.1787.

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Example 5
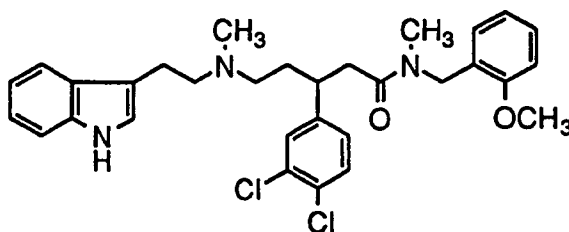
Step 1:   Combine 3,4-dichlorobenzaldehyde (100 g) in 95%
CH3CH2OH (120 mL) with ethylacetoacetate (146 mL) and stir until a
5   homogenous solution is obtained. Treat this solution with piperidine (8
mL) and allow to stand for 18 hours. Recrystallize the crude product from
95% ethanol to give diethyl-3,4-dichlorobenzal-*bis*-acetoacetate (230 g).
Step 2:   Reflux the product of Step 1 (155 g) in CH3CH2OH (2 L) and
50% NaOH (2 l) for 4 hours. Add water (1 L) to the reaction mixture and
10   remove approx. 1.5 L of solvent by distillation. Pour the remaining
solution onto ice (1 Kg) and add sufficient HCl to adjust the pH to 1.
Extract the resulting solution with EtOAc (3 X 1.5 L), dry the combined
extracts over MgSO4, filter and concentrate to give 100 g of 3-(3,4-
dichlorophenyl)-glutaric acid.
15   Step 3:   Heat a combination of the product of Step 2 (100 g) and
acetyl chloride (300 mL) at reflux for 5 hours. Cool the reaction mixture,
azeotrope with toluene, and concentrate under reduced pressure. Slurry
the residue with Et2O (250 mL) and filter to afford 3-(3,4-dichlorophenyl)-
glutaric anhydride (86 g).
20   Step 4:   Sequentially treat the product of Step 3 (5.9 g) in CH2Cl2 (80
mL) at 0°C with N-methyl-N-[2-(methoxyphenyl)methyl]amine (3.8 g), Et3N
(3.5 mL) and DMAP (278 mg). Stir the mixture at 0°C for 2 h, allow to
warm to room temperature and stir for 20 h. Wash the reaction mixture
with 1N HCl (1 x 100 mL) and brine (1 x 100 mL), dry the organic layers
25   over MgSO4, filter and concentrate to afford 3,4-dichloro-β-[2-[[(2-methoxy-
phenyl)methyl]-methylamino]-2-oxoethyl] benzenepropanoic acid (9.3 g).
Step 5:   Treat the acid from Step 4 (9.3 g) in EtOAc (100 mL) with
1,1'-carbonyldiimidazole (4.62 g) and DMAP (345 mg), stir the resulting
solution at room temperature for 15 min., then heat at 50°C for 1 h. Cool
30   the reaction mixture to 0°C and treat with a solution of NaBH4 (3.45 g) in
H2O (50 mL), warm slowly to room temperature and stir for 12 h. Dilute
the reaction mixture with EtOAc (250 mL) and wash with 1N HCl (1 x 100

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mL) and H₂O (1 x 100 mL), dry over MgSO₄, filter and concentrate under reduced pressure to yield a crude oil (13 g). Chromatograph on silica gel, eluting with 5% CH₃OH/CH₂Cl₂ to give 3,4-dichloro-β-(2-hydroxyethyl)-N-methyl-N-[(2-methoxyphenyl) methyl]benzenepropanamide (8.7 g).

5   HRMS (FAB, M+H+): m/e cal'd for [C$_{20}$H$_{24}$NO$_3$Cl$_2$]$^+$ 396.1133; found 396.1124.

Step 6:   Cool a solution of oxalyl chloride (1.43 mL) in CH₂Cl₂ (30 mL) to -78°C, add DMSO (2.32 mL) dropwise over 15 mins., stir for 15 min., then add a CH₂Cl₂ (20 mL) solution of the product of Step 5 (1.3 g)

10   over 20 min. Stir the mixture for 30 min, treat with Et₃N (9.2 mL) and stir for an additional 30 min. at -78°C, followed by 1.5 h at room temperature. Quench the reaction mixture with water and dilute with CH₂Cl₂ (100 mL). Separate the organic fraction, wash sequentially with 1N HCl (1 x 50 mL), sat. NaHCO₃ (1 x 50 mL) and brine (1 x 50 mL), dry over MgSO₄, filter and

15   concentrate under reduced pressure to yield an oil. Chromatograph on silica gel, eluting with 50-100% EtOAc/hexane to give 3,4-dichloro-β-(2-oxoethyl)-N-methyl-N-[(2-methoxyphenyl)methyl] benzenepropanamide (950 mg).

Step 7:   Sequentially treat the aldehyde of Step 6 (770 mg), in 2,2,2-
20   trifluoroethanol (5 mL) with molecular sieves 3A (510 mg), N-ω-methyltryptamine (510 mg) and NaCNBH₃ (123 mg). Stir the resulting mixture at room temperature for 18 h., dilute the reaction mixture with EtOAc (50 mL) and filter through silica gel. Concentrate the resulting organic layer under reduced pressure to give the crude product as an oil.

25   Chromatograph on silica gel, eluting with 10% MeOH/CH₂Cl₂ gave the title compound (525 mg). HRMS (FAB, M+H+): m/e cal'd for [C$_{21}$H$_{35}$N$_3$O$_2$Cl$_2$]$^+$ 552.2185; found: 552.2179.
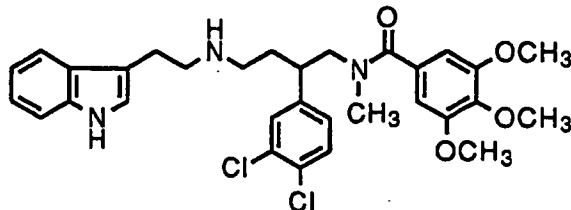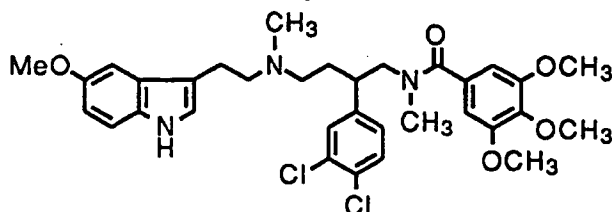
Example 6
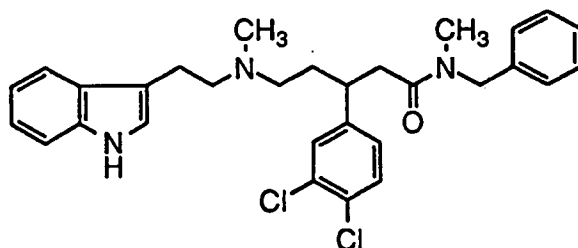
30   The compound of Example 6 is prepared by a procedure similar to that descruibed in Example 5 except using N-methyl-N-phenyl-methylamine in place of N-methyl-N-[2-(methoxyphenyl)methyl]amine.

MS (FAB, M+H+): *m/e* 522; Analysis for $C_{30}H_{33}Cl_2N_3O \cdot 0.5H_2O$: Found: C, 67.84; H, 6.43; N, 7.90; calc'd C, 67.79; H, 6.45; N, 7.91%.
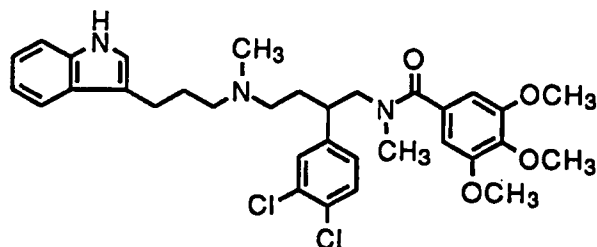
Example 7

5   Step 1: To a -55°C solution of oxalyl chloride (2.25 mL, 25.8 mmol) in CH_2Cl_2 (45 mL), slowly add a solution of DMSO (2.4 mL, 33.8 mmol) in CH_2Cl_2 (45 mL) followed by a solution of the alcohol from Example 2, Step 3 (7.55 g, 17.1 mmol) in CH_2Cl_2 (90 mL). Stir for 30 min. at -55°C, add Et_3N (9.2 mL, 66 mmol) and stir for 2h at -55°C. Add 20% sat. $KHSO_4$
10 (75 mL) and Et_2O (100 mL), warm to room temperature and stir for 30 min. Add to Et_2O (225 mL) and remove the aqueous layer, wash with sat. $NaHCO_3$ (2 x 100 mL), H_2O (100 mL) and brine (100 mL). Dry the solution with $MgSO_4$ and concentrate to give 7.36 g of desired aldehyde product as a white foam (16.7 mmol, 98 %).

15 Step 2: Treat a solution of the product from step 1 (2.48 g, 5.6 mmol), tryptamine (1.44 g, 9.0 mmol) and crushed 3A mol. sieves (1.66 g) in CF_3CH_2OH (50 mL) with $NaCNBH_3$ (1.57 g, 25 mmol). Stir the reaction mixture for 30 min, filter and concentrate. Chromatograph the crude product on silica gel, eluting with 25:10:1 to 10:1:0.1 CH_2Cl_2:MeOH:NH$_3$
20 (aq.) to give 2.43 g of product as a white foam (4.16 mmol, 74 %).
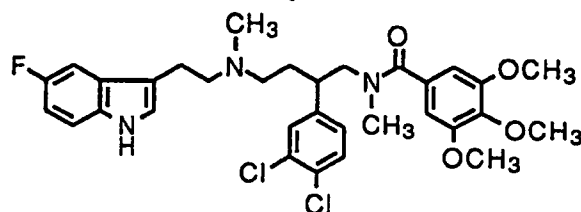MS (FAB, M+H+): m/e 584.

Example 7a

Using the procedure of Example 7, substitute 5-methoxy-Nω-
25 methyltryptamine for Nω-methyltryptamine in step 2 to obtain the title compound.
HRMS (FAB, M+H+): m/e calc'd for $[C_{33}H_{40}N_3O_5Cl_2]^+$ 628.2345; found 628.2345.
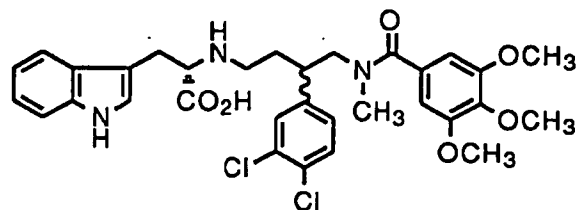
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Example 7b

Using the procedure of Example 7, substitute 3-(N-methyl-3-aminopropyl)indole for Nω-methyltryptamine in step 2 to obtain the title compound.

HRMS (FAB, M+H+): m/e calc'd for $[C_{33}H_{40}N_3O_4Cl_2]^+$ 612.2396; found 612.2399.

Example 7c

Using the procedure of Example 7, substitute 5-fluoro-Nω-methyltryptamine for Nω-methyltryptamine in step 2 to obtain the title compound.

HRMS (FAB, M+H+): m/e calc'd for $[C_{32}H_{37}N_3O_4Cl_2F]^+$ 616.2145; found 616.2148.

Separate the product of Example 7c into its enantiomers by chiral preparative HPLC using a Chiralpak AS column, eluting with 80:20 to 75:25 hexane:i-propylalcohol. The second enantiomer to elute has an optical rotation of $[\alpha]_D^{25}$ = +8.8° (c= 4.4g/l in CH$_3$OH)

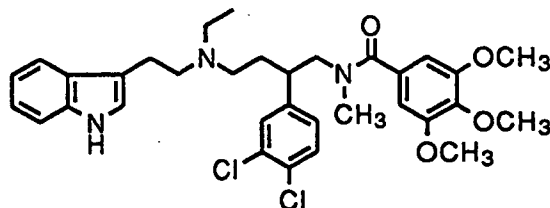### Example 7d

Using the procedure of Example 7, substitute L-tryptophan for Nω-methyltryptamine in step 2 to obtain the title compound.
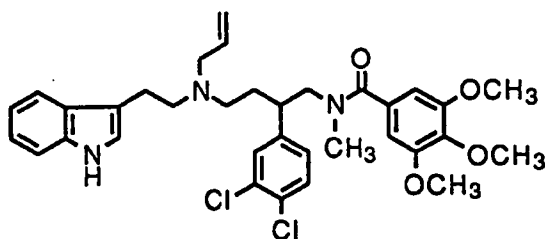
MS (FAB, M+H+): m/e 628.

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Example 8
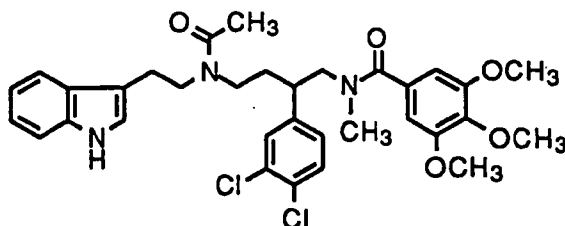
Treat a solution of the product from Example 7 (144.8 mg, 0.248 mmol) and pyridine (30 µL, 0.37 mmol) in CH_2Cl_2 (1.5 mL) with acetic
5   anhydride (23.5 µL, 0.25 mmol) and stir for 35 min. Add the reaction mixture to 0.2 N HCl (25 mL) and extract with CH_2Cl_2 (3 x 10 mL). Wash the combined organic layers with sat. $NaHCO_3$ (10 mL) and brine (10 mL), dry with $MgSO_4$, and concentrate. Chromatograph on silica gel, eluting with 20:1 CH_2Cl_2:CH_3OH, to obtain 127 mg of the desired product as a
10   white foam (0.2 mmol, 82 %).
HRMS (FAB, M+H+): m/e calc'd for $[C_{33}H_{38}N_3O_5Cl_2]^+$ 626.2189; found 626.2181.

Example 9

15   Treat a solution of the product from Example 7 (63.5 mg, 0.109 mmol) and CH_3CH_2I (10 µL, 0.13 mmol) in DMF (1.1 mL) with 50% KF-celite (40.7 mg) and stir at 60°C overnight. Add the reaction mixture to H_2O (50 mL) and extract with EtOAc (3 x 25 mL). Wash the combined organic layers with brine (25 mL), dry with $MgSO_4$, and concentrate.
20   Chromatograph on silica gel, eluting with 10:1 CH_2Cl_2:CH_3OH:NH_3 (aq), to obtain 42.7 mg of the product as a white foam (0.07 mmol, 64 %).
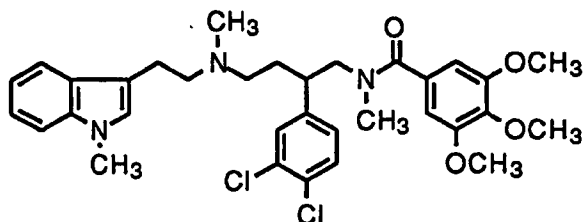HRMS (FAB, M+H+): m/e calc'd for $[C_{33}H_{40}N_3O_4Cl_2]^+$ 612.2396; found 612.2405.

Example 9b

25

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Using the procedure of Example9, substitute allyl bromide for CH3CH2I to obtain the title compound.

HRMS (FAB, M+H+): m/e calc'd for [C34H40N3O4Cl2]+ 624.2396; found 624.2385.

Example 9c

Use a procedure similar to Example 9, substituting CH3I (2 equivalents) for the alkylating agent and NaH for the base to obtain the title compound. HRMS (FAB, M+H+): m/e calc'd for [C33H40N3O4Cl2]+ 612.2396; found 612.2407.

The following compound is isolated as a side product from the previous reaction:
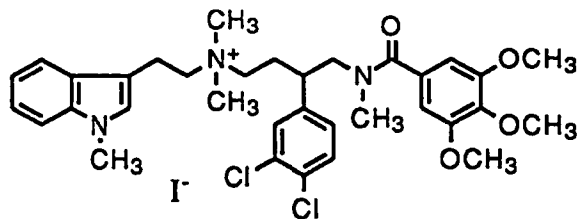
HRMS (FAB, M): m/e calc'd for [C34H42N3O4Cl2]+ 626.2552; found 626.2564.
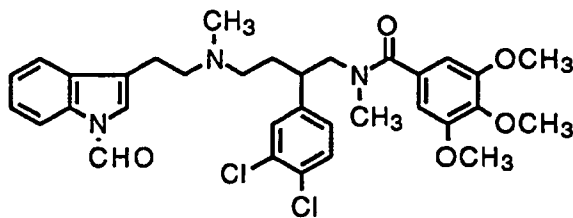
Example 10

Treat the product of Example 2 (49.3 mg, 82 μmol) with formic acid (750 μL, 20 mmol) and acetic anhydride (30 mL, 0.32 mmol) and heat at 70°C for 3 days. Add the reaction mixture to H2O (50 mL) and extract with CH2Cl2 (2 x 35 mL). Wash the combined organic layers with brine (25 mL), dry with MgSO4 and concentrate. Chromatograph on silica gel, eluting with 20:1 to 10:1 CH2Cl2:CH3OH:NH3 (aq), to obtain 9.3 mg of the desired product as a white foam. HRMS (FAB, M+H+): m/e calc'd for [C33H38N3O5Cl2]+ 626.2187; found 626.2189.

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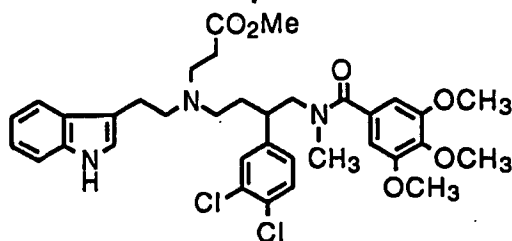
Example 11

Step 1: Treat a solution of the product of Example 7 (115.1 mg, 0.197 mmol) in DMF (2.0 mL) with methyl acrylate (30 µL, 0.33 mmol) and stir at

5   60°C overnight. Add additional methyl acrylate (20 µL, 0.22 mmol) to the reaction mixture and stir at 60°C for 24 h. Add the reaction mixture to H_2O (50 mL) and extract with EtOAc (3 x 25 mL). Wash the combined organic layers with brine (25 mL), dry with $MgSO_4$, and concentrate. Chromatograph on silica gel, eluting with 25:1 CH_2Cl_2:CH_3OH, to obtain

10   66.9 mg of the desired product (0.10 mmol, 51 %). HRMS (FAB, M+H+): m/e calc'd for $[C_{35}H_{42}N_3O_6Cl_2]^+$ 670.2451; found 670.2447.

Example 12
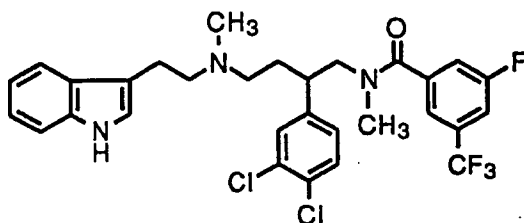
15   Step 1: Heat a solution of the product of Example 1, step 4 (5.8 g, 17 mmol) in ethyl formate (100 mL) at reflux for 65 h and concentrate. Chromatograph on silica gel, eluting with 1:1 hexane:EtOAc, to obtain 4.4 g of the desired formamide as a colorless oil (12 mmol, 72 %).

Step 2: Treat a solution of the product of step 1 (4.2 g, 11.6 mmol) in Et_2O

20   (25 mL) with BH_3.DMS (7.5 mL, 75 mmol) and stir at ambient temperature for 24 h. After concentrating the reaction mixture, quench the excess BH_3.DMS by the careful addition of CH_3OH. Add HCl-saturated CH_3OH to the resulting mixture, heat at 60°C for 1 h and concentrate to give 3.08 g of N-methyl-4-amino-3-(3,4-dichlorophenyl)-butanol.

25   Step 3: Treat the crude product of step 2 (3.08 g) with K_2CO_3 (3.02 g) and $(BOC)_2O$ (3.43 g, 15.7 mmol) in CH_3OH (30 mL) for 2.5 h, filter and concentrate. Chromatograph on silica gel, eluting with 1:1 hexane:EtOAc, to obtain 2.50 g of the BOC-protected product (7.2 mmol, 62 % for 2 steps).
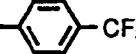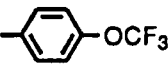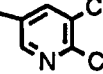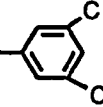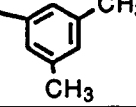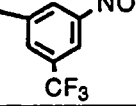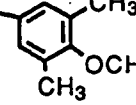
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<u>Step 4:</u> To a -55°C solution of oxalyl chloride (0.94 mL, 10.8 mmol) in
CH_2Cl_2 (20 mL), slowly add DMSO (1.0 mL, 14.1 mmol) followed by a
solution of the alcohol from step 3 (2.50 g, 7.2 mmol) in CH_2Cl_2 (35 mL).
After stirring for 30 min. at -55°C, add Et_3N (4.0 mL, 29 mmol) and stir for

5   2h at -55°C. Add 20% sat. $KHSO_4$ (28 mL) and Et_2O (35 mL), warm to
room temperature and stir for 30 min. Add to Et_2O (100 mL), remove the
aqueous layer, wash with sat. $NaHCO_3$ (3 x 35 mL), H_2O (35 mL) and
brine (35 m). Dry the solution with $MgSO_4$ and concentrate to give 2.5 g of
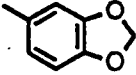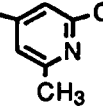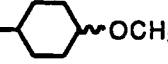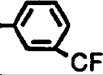desired aldehyde product (quantitative yield).

10 <u>Step 5:</u> Treat a solution of the product of step 4 (2.50 g, 7.2 mmol), N-
methyl tryptamine (13.8 mmol) and crushed 3A mol. sieves (2.0 g) in
CF_3CH_2OH (25 mL) with $NaCNBH_3$ (1.75 g, 27.8 mmol). Stir for 1 h, add
H_2O (250 mL) and extract with 2:1 CH_2Cl_2:Et_2O (3 x 150 mL). Wash the
combined organic layers with brine (150 mL), dry with $MgSO_4$ and

15 concentrate. Chromatograph the crude product on silica gel, eluting with
10:1:0.1 CH_2Cl_2:CH_3OH:NH_3 (aq.) to give 2.5 g of product as a white
foam (5.0 mmol, 69 %).

<u>Step 6:</u> Treat the product of step 5 (4.5 g, 8.9 mmol) with trifluoroacetic
acid (30 mL) for 2 h and concentrate. Suspend the residue in saturated

20 $NaHCO_3$ and extract with CH_2Cl_2. Wash the combined organic layers
with brine, dry with $MgSO_4$ and concentrate. Chromatograph on silica gel,
eluting with 10 to 20 % NH_3 saturated CH_3OH:CH_2Cl_2, to obtain 2.0 g of
the amino product as a white solid (4.9 mmol, 55 %).

<u>Step 7:</u> Convert the product from step 6 to the title compound using a

25 procedure similar to that described in Example 2, Step 1, substituting
3,4,5-trimethoxybenzoic acid for 3-fluoro-5-trifluromethylbenzoic acid.
HRMS (FAB, M+H+): m/e calc'd for $[C_{30}H_{30}N_3OCl_2F_4]^+$ 594.1702; found
594.1702.

Using the procedure of Example 12, substitute the

30 appropriate acid in step 7 to obtain the compounds of the following
structure, wherein W is as shown in the table:
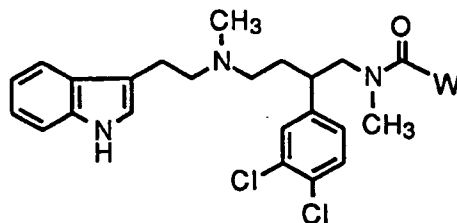
Ex.	W	HRMS (FAB, M+H+): m/e calc'd	HRMS (FAB, M+H+): m/e found
12a	(methyl-benzodioxole)	552.1821	552.1816
12c	(2-chloro-6-methylpyridin-4-yl)	557.1642	557.1644
12d	(4-methoxymethyl-cyclohexyl)	544.2498	544.2499
12e	(3-CF₃-phenyl)	576.1796	576.1796
12f	(4-CF₃-phenyl)	576.1796	576.1792
12g	(4-OCF₃-phenyl)	592.1745	592.1746
12h	(3,2-dichloropyridin-5-yl)	577.1095	577.1087
12i	(3,5-dichlorophenyl)		MS (FAB, M+H+): m/e 576
12j	(3,5-dimethylphenyl)	536.2235	536.2249
12k	(3-NO₂-5-CF₃-phenyl)	621.1647	621.1646
12l	(2,4-dimethyl-3-methoxyphenyl)	566.2341	566.2345

Example 13
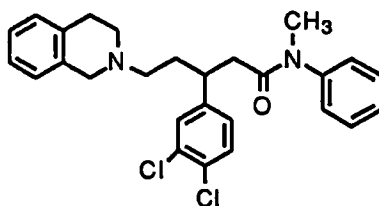
Treat 3,4-dichloro-beta-(2-oxoethyl)-N-methyl-N-phenylbenzenepropanamide (0.53 g) in CH₃OH (35 mL) sequentially with molecular sieves 3A (5.5 g), isoquinoline HCl (0.33 g) and NaBH₃CN (0.4

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g). Stir the resulting mixture at room temperature for 20 hours, filter
through a pad of celite and concentrate under reduced pressure. Partition
the residue between 10% NH_4OH solution and CH_2Cl_2 (25 mL), separate
the organic layer and extract the aqueous layer with CH_2Cl_2 (2X25 mL).
5   Dry the combined organic layers over $MgSO_4$, filter and concentrate under
reduced pressure to give a crude oil (0.7 g). Chromatograph on silica gel,
eluting with 2% CH_3OH/CH_2Cl_2 to obtain the title compound (0.27 g).
Mass spectrum (FAB): 467.

Example 14
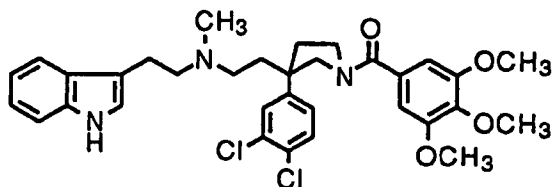
10

Use 3-(3,4-dichlorophenyl)-3-(2-hydroxyethyl)-pyrrolidine in the
procedure of Example 12, steps 3-7, substituting 3,4,5-trimethoxybenzoic
acid for 3-fluoro-5-trimethylbenzoic acid to obtain the title compound.
HRMS (FAB, M+H+): m/e calc'd for $[C_{33}H_{37}N_3O_4Cl_2]^+$ 610.2239; found
15   610.2219.

Example 14a
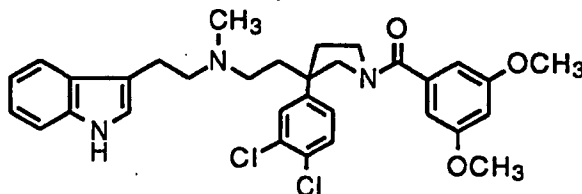
Use the procedure of Example 14, substituting 3,5-dimethoxy-
benzoic acid for 3,4,5-trimethoxybenzoic acid to obtain the title compound.
20   HRMS (FAB, M+H+): m/e calc'd for $[C_{32}H_{36}N_3O_3Cl_2]^+$ 580.2134; found
580.2116.

Example 14b
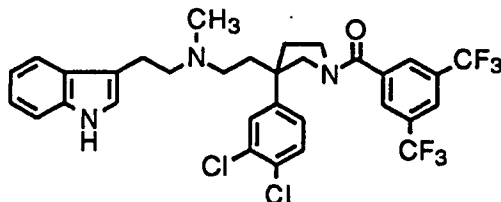
Using the procedure of Example 14, substitute 3,5-bis(trifluoro-
25   methyl)benzoic acid for 3,4,5-trimethoxybenzoic acid to obtain the title
compound. HRMS (FAB, M+H+): m/e calc'd for $[C_{32}H_{30}N_3OCl_2F_6]^+$
656.1670; found 656.1663.

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The following formulations exemplify some of the dosage forms of this invention. In each, the term "active compound" refers to a compound of formula I.

EXAMPLE A
Tablets

No.	Ingredient	mg/tablet	mg/tablet
1	Active Compound	100	500
2	Lactose USP	122	113
3	Corn Starch, Food Grade, as a 10% paste in Purified Water	30	40
4	Corn Starch, Food Grade	45	40
5	Magnesium Stearate	<u>3</u>	<u>7</u>
	Total	300	700

Method of Manufacture

Mix Item Nos. 1 and 2 in suitable mixer for 10-15 minutes. Granulate the mixture with Item No. 3. Mill the damp granules through a coarse screen (e.g., 1/4", 0.63 cm) if necessary. Dry the damp granules. Screen the dried granules if necessary and mix with Item No. 4 and mix for 10-15 minutes. Add Item No. 5 and mix for 1-3 minutes. Compress the mixture to appropriate size and weight on a suitable tablet machine.

EXAMPLE B
Capsules

No.	Ingredient	mg/tablet	mg/tablet
1	Active Compound	100	500
2	Lactose USP	106	123
3	Corn Starch, Food Grade	40	70
4	Magnesium Stearate NF	<u>4</u>	<u>7</u>
	Total	250	700

Method of Manufacture

Mix Item Nos. 1, 2 and 3 in a suitable blender for 10-15 minutes. Add Item No. 4 and mix for 1-3 minutes. Fill the mixture into suitable two-piece hard gelatin capsules on a suitable encapsulating machine.

EXAMPLE C
Sterile Powder for Injection

Ingredient	mg/vial	mg/vial
Active sterile powder	100	500

For reconstitution add sterile water for injection or bacteriostatic water for injection.

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The *in vitro* and *in vivo* activity of the compounds of formula I can be determined by the following procedures.

In vitro procedure to identify NK$_1$ activity

5   Test compounds are evaluated for their ability to inhibit the activity of the NK$_1$ agonist Substance P on the isolated guinea pig vas deferens. Freshly cut vas deferens are removed from male Hartley guinea pigs (230-350g) and suspended in 25 ml tissue baths containing Kreb's Henseleit solution warmed to 37°C and constantly aerated with 95% O$_2$ and 5% CO$_2$. Tissues are adjusted to 0.5 g and allowed to equilibrate for

10   a period of 30 minutes. The vas deferens are exposed to an electrical field stimulation (Grass S48 Stimulator) every 60 seconds at an intensity that will cause the tissue to contract 80% of its maximum capacity. All responses are recorded isometrically by means of a Grass force displacement transducer (FT03) and Harvard electronic recorder.

15   Substance P inhibits the electrical field stimulated-induced contractions of the guinea pig vas deferens. In unpaired studies, all tissues (control or drug treated) are exposed to cumulative concentations of Substance P ($1X10^{-10}$ M - $7X10^{-7}$ M). Single log-concentations of the test compounds are given to separate tissues and allowed to equilibrate for 30 minutes

20   before a Substance P concentration-response curve is generated. At least 5 separate tissues are used for each control and individual drug-concentation for every drug assay.

Inhibition of the Substance P is demonstrated by a rightward shift of its concentration-response curve. These shifts are used to

25   determine the pA$_2$ value, which is defined as the negative log of the molar concentration of the inhibitor which would require that twice as much agonist be used to elicit a chosen response. This value is used to determine relative antagonist potency.

Isolated Hamster Trachea NK$_2$ Assay

30   General methodology and characterization of hamster trachea responses to neurokinin agonists as providing an NK$_2$ monoreceptor assay is found in C.A. Maggi, et al., *Eur. J. Pharmacol.* 166 (1989) 435 and J.L. Ellis, et al., *J. Pharm. Exp. Ther.* 267 (1993) 95.

Continuous isometric tension monitoring is achieved with

35   Grass FT-03 force displacement transducers connected to Buxco Electronics preamplifiers built into a Graphtec Linearcorder Model WR 3310.

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Male Charles River LAK:LVG (SYR) hamsters, 100-200 g fed
weight, are stunned by a sharp blow to the head, loss of corneal reflex is
assured, the hamsters are sacrificed by thoractomy and cutting the heart.
Cervical trachea segments are removed to room temperature Krebs buffer,

5   pH 7.4, aerated with 95% O_2 - 5% CO_2 gas and cleaned of adhering
tissue. The segments are cut into two 3-4 mm long ring segments.
Tracheal rings are suspended from transducers and anchored in 15.0 ml
water jacketed organ baths by means of stainless steel hooks and 6-0 silk.
Baths are filled with Krebs buffer, pH 7.4, maintained at 37°C and

10   continuously aerated with 95% O_2 - 5% CO_2 gas. Tracheal rings are
placed under 1.0 g initial tension and allowed a 90 min equilibration
period with four 1 μM NKA challenge, wash and recovery cycles at 20 min
intervals. 30 min vehicle pretreatment is followed by cumulative additions
of rising doses of NKA (3 nM - 1 μM final concentration, 5 min intervals

15   between additions). The final NKA response is followed by a 15 min wash
and recovery period. 30 min pretreatment with a test compound or its
vehicle is followed by cumulative additions of rising doses of NKA (3 nM -
10 μM final concentration if necessary, 5 min intervals between additions).
The final NKA response is followed by a 1 mM carbachol challenge to

20   obtain a maximal tension response in each tissue.

Tissue responses to NKA are recorded as positive pen
displacements over baseline and converted to grams tension by
comparison to standard weights. Responses are normalized as a % of the
maximal tissue tension. ED_{50}'s are calculated for NKA from the control

25   and treated NKA dose responses and compared. Test compounds
resulting in an agonist dose ratio ≥ 2 at a screening concentration of 1 μM
(i.e. $pA_2 \geq$ = 6.0) are considered actives. Further dose response data is
obtained for actives so that an apparent pA_2 estimate can be calculated.
pA_2 is calculated either by estimation of K_i as described by Furchgott

30   (where pA_2 = - Log K_i, R.F. Furchgott, *Pharm. Rev.* 7 [1995] 183) or by
Shild Plot Analysis (O. Arunlakshana & H.O. Shild, *Br. J. Pharmacol.*
14[1959] 48) if the data is sufficient.

**Effect of NK_1 Antagonists on Substance P-Induced Airway
Microvascular Leakage in Guinea Pigs**

35   Studies are performed on male Hartley guinea pigs ranging
in weight from 400-650 g. The animals are given food and water *ad
libitum*. The animals are anesthetized by intraperitoneal injection of
dialurethane (containing 0.1 g/ml diallylbarbituric acid, 0.4 g/ml ethylurea

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and 0.4 g/ml urethane). The trachea is cannulated just below the larynx and the animals are ventilated (V_T = 4 ml, f = 45 breaths/min) with a Harvard rodent respirator. The jugular vein is cannulated for the injection of drugs.

5   The Evans blue dye technique (Danko, G. et al., Pharmacol. Commun., 1, 203-209, 1992) is used to measure airway microvascular leakage (AML). Evans blue (30 mg/kg) is injected intravenously, followed 1 min later by i.v. injection of substance P (10 µg/kg). Five min later, the thorax is opended and a blunt-ended 13-guage needle passed into the

10 aorta. An incision is made in the right atrium and blood is expelled by flushing 100 ml of saline through the aortic catheter. The lungs and trachea are removed en-bloc and the trachea and bronchi are then blotted dry with filter paper and weighed. Evans blue is extracted by incubation of the tissue at 37°C for 18 hr in 2 ml of formamide in stoppered tubes. The

15 absorbance of the formamide extracts of dye is measured at 620 nm. The amount of dye is calculated by interpolation from a standard curve of Evans blue in the range 0.5-10 µg/ml in formamide. The dye concentration is expressed as ng dye per mg tissue wet weight. Test compounds were suspended in cyclodextran vehicle and given i.v. 5 min

20 before substance P.

Measurement of NK₂ Activity In Vivo

         Male Hartley guinea pigs (400-500 gm) with ad lib. access to food and water are anesthetized with an intraperitoneal injection of 0.9 ml/kg dialurethane (containing 0.1 g/m diallylbarbituric acid, 0.4 g/ml

25 ethylurea and 0.4 g/ml urethane). After induction of a surgical plane of anesthesia, tracheal, esophageal and jugular venous cannulae are implanted to facilitate mechanical respiration, measurement of esophageal pressure and administration of drugs, respectively.

         The guinea pigs are placed inside a whole body

30 plethysmograph and the catheters connected to outlet ports in the plethysmograph wall. Airflow is measured using a differential pressure transducer (Validyne, Northridge CA, model MP45-1, range ± 2 cmH₂O) which measures the pressure across a wire mesh screen that covers a 1 inch hole in the wall of the plethysmograph. The airflow signal is

35 electrically integrated to a signal proportional to volume. Transpulmonary pressure is measured as the pressure difference between the trachea and the esophagus using a differential pressure transducer (Validyne, Northridge, CA, model MP45-1, range ± 20 cm H₂O). The volume, airflow

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and transpulmonary pressure signals are monitored by means of a
pulmonary analysis computer (Buxco Electronics, Sharon, CT, model 6)
and used for the derivation of pulmonary resistance (R_L) and dynamic
lung compliance (C_{Dyn}).

5   Bronchoconstriction Due to NKA

Increasing iv doses of NKA are administered at half log
(0.01-3 µg/kg) intervals allowing recovery to baseline pulmonary
mechanics between each dose. Peak bronchoconstriction occurs within
30 seconds after each dose of agonist. The dose response is stopped

10   when C_{Dyn} is reduced 80-90% from baseline. One dose-response to NKA
is performed in each animal. Test compounds are suspended in
cyclodextran vehicle and given i.v. 5 min before the initiation of the NKA
dose response.

For each animal, dose response curves to NKA are

15   constructed by plotting the percent increase in R_L or decrease in C_{Dyn}
against log dose of agonist. The doses of NKA that increased R_L by 100%
(R_L100) or decreased C_{Dyn} by 40% ($C_{Dyn}40$) from baseline values are
obtained by log-linear interpolation of the dose response curves.

Neurokinin Receptor Binding Assay(s)

20   Chinese Hamster ovary (CHO) cells transfected with the
coding regions for the human neurokinin 1 (NK1) of the human neurokinin
2 (NK2) receptors are grown in Dulbecco's minimal essential medium
supplemented with 10% fetal calf serum, 0.1 mM non-essential amino
acids, 2 mM glutamine, 100units/ml of penicillin and streptomycin, and 0.8

25   mg of G418/ml at 37°C in a humidified atmosphere containing 5% CO_2.

Cells are detached from T-175 flasks with a sterile solution
containing 5mM EDTA in phosphate buffered saline. Cells are harvested
by centrifugation and washed in RPMI media at 40°C for 5 minutes. The
pellet is resuspended inTris-HCl (pH7.4) containing 1 uM phsphoramidon

30   and 4 ug/ml of chymostatin at a cell density of 30 x 10^6 cells/ml. The
suspension is then homogenized in a Brinkman Polytron (setting 5) for 30-
45 seconds. The homogenate is centrifuged at 800 x g for 5 min at 4°C to
collect unbroken cells and nuclei. The supernatant is centrifuged in a
Sorvall RC5C at 19,000 rpm (44,00 x g) for 30 min at 4°C. The pellet is

35   resuspended, an aliquot is removed for a protein determination (BCA) and
washed again. The resulting pellet is stored at -80°C.

To assay receptor binding, 50 µl of [^{3}H]-Substance P (9-Sar,
11-Met [02]) (specific activity 41 Ci/mmol) (Dupont-NEN) (0.8 nM for the

NK-1 assay) or [^{3}H]-Neurokinin A (specific activity 114 Ci/ mmole) (Zenca) (1.0 nM for the NK-2 assay) is added to tubes containing buffer (50 mM Tris-HCl (pH 7.4) with 1 mM MnCl$_2$ and 0.2% Bovine Serum Albumin) and either DMSO or test compound. Binding is initiated by the addition of

5   100µl of membrane (10-20 µg) containing the human NK-1 or NK-2 receptor in a final volume of 200 µl. After 40 minutes at room temperature, the reaction is stopped by rapid filtration onto Whatman GF/C filters which have been presoaked in 0.3% polyethylenimine. Filters are washed 2 times with 3 ml of 50 mM Tris-HCl (pH7.4). Filters are added to 6 mls of

10   Ready-Safe liquid scintillation cocktail and quantified by liquid scintillation spectrometry in a LKB 1219 RackBeta counter. Non-specific binding is determined by the addition of either 1 µM of CP-99994 (NK-1) or 1µM SR-48968 (NK-2) (both synthesized by the chemistry department of Schering-Plough Research Institute). IC$_{50}$ values are determined from competition

15   binding curves and Ki values are determined according to Cheng and Prusoff using the experimentally determined value of 0.8 nM for the NK-1 receptor and 2.4 nM for the NK-2 receptor.

NK$_3$ activity is determined by following a procedure similar to that described in the literature, e.g., *Molecular Pharmacol.*, 48 (1995), p.

20   711-716.

% Inhibition is the difference between the percent of maximum specific binding (MSB) and 100%. The percent of MSB is defined by the following equation, wherein "dpm" is disintegrations per minute:

$$\% \ MSB = \frac{(dpm \ of \ unknown) - (dpm \ of \ nonspecific \ binding)}{(dpm \ of \ total \ binding) - (dpm \ of \ nonspecific \ binding)} \ X \ 100$$

25

It will be recognized that compounds of formula I exhibit NK$_1$, NK$_2$ and/or NK$_3$ antagonist activity to varying degrees, e.g., certain compounds have strong NK$_1$ antagonist activity, but weaker NK$_2$ and NK$_3$ antagonist activity, while others are strong NK$_2$ antagonists, but weaker

30   NK$_1$ and NK$_3$ antagonists. While compounds with approximate equipotency are preferred, it is also within the scope of this invention to use compounds of with unequal NK$_1$/NK$_2$/NK$_3$ antagonist activity when clinically appropriate.

Using test procedures described above, the following data

35   (% inhibition or Ki) were obtained for preferred and/or representative compounds of formula I:

Ex.	% Inhibition NK$_1$ (1μM dose)	Ki (NK$_1$) (nM)	% Inhibition NK$_2$ (1μM dose)	Ki (NK$_2$) (nM)	Ki (NK$_3$) (nM)
7c	--	12	100	10	--
7d	--	233	--	30	--
9b	--	23	--	250	--
12a	69	165	96	59	--
12k	--	30	--	39	--
14a	--	233	--	30	--
2	81	25	87	33	448

Compounds of the present invention exhibit a range of activity: percent inhibition at a dosage of 1μM ranges from about 0 to about 100% inhibition of NK$_1$ and/or about 0 to about 100% inhibition of NK$_2$. Preferred are compounds having a Ki ≤100nM for the NK$_1$ receptor.

5 Also preferred are compounds having a Ki ≤100nM for the NK$_2$ receptor. Another group of preferred compounds are those having a Ki ≤100nM for each of the NK$_1$ and NK$_2$ receptors.

We claim:

1.   A compound represented by the structural formula
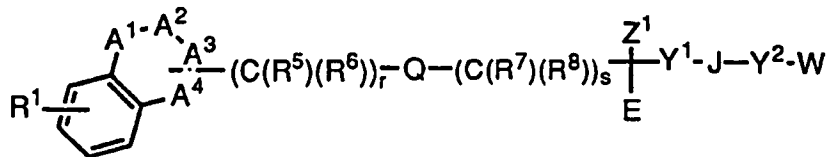
I

or a pharmaceutically acceptable salt thereof, wherein:

A^1, A^2, A^3 and A^4 are independently selected from the group consisting of $-(C(R^2)(R^{10}))-$, $-(C(R^{2c})(R^{10}))-$, $-(C(R^2))=$, $-(C(R^{2c}))=$, $-NR^{16}-$, $-N=$, $-O-$, $-S(O)_e-$, $-C(O)-$ and a bond, wherein A^1, A^2, A^3 and A^4, together with the carbon atoms to which they are attached, form a 5- or 6-membered ring, and wherein two adjacent A groups are selected from the group consisting of the following combinations:

$-(C(R^2)(R^{10}))-(C(R^2)(R^{10}))-$;

$-(C(R^2)(R^{10}))-(C(R^{2c}))=$;

$-(C(R^{2c})(R^{10}))-NR^{16}-$;

$-(C(R^{2c})(R^{10}))-N=$;

$-(C(R^{2c})(R^{10}))-O-$;

$-(C(R^{2c})(R^{10}))-S(O)_e-$;

$-(C(R^2)(R^{10}))-C(O)-$;

$-(C(R^2))=(C(R^2))-$;

$-(C(R^2))=N-$;

$=(C(R^2))-(C(R^2))=$;

$=(C(R^2))-NR^{16}-$;

$=(C(R^2))-N=$;

$=(C(R^2))-O-$;

$=(C(R^2))-S(O)_e-$;

$=(C(R^2))-C(O)-$;

$-NR^{16}-N=$;

$-NR^{16}-S(O)_e-$;

$-NR^{16}-C(O)-$;

$-N=N-$;

$=N-N=$;

$=N-O-$;

$=N-S(O)_e-$;

$=N-C(O)-$;

$-O-S(O)_e-$; and

-O-C(O)-;

provided that three adjacent A groups do not represent -C(O)-O-C(O)-, -S(O)-O-C(O)- or -S(O)-O-S(O)-, and provided that when an aromatic nitrogen is present in the ring formed by A^1, A^2, A^3 and A^4, the N-oxide

5 can be formed;

E is R^3-aryl or R^3-heteroaryl;

W is R^4-cycloalkyl, R^4-aryl, R^4-heterocycloalkyl or R^4-heteroaryl;

R^1, R^3 and R^4 are independently 1-3 substituents

10 independently selected from the group consisting of H, halogeno, C_1-C_6 alkyl, -CF_3, -C_2F_5, -OR^{11}, -COR^{11}, -CO_2R^{11}, -$CON(R^{11})(R^{12})$, -$N(R^{11})(R^{12})$, -$N(R^{11})COR^{12}$, -SH, -$S(O)_eR^{13}$, -$OC(O)R^{11}$, -$OC(O)N(R^{11})(R^{12})$, -$NR^{11}CO_2R^{13}$, -$NR^{11}C(O)N(R^{12})(R^{14})$, R^{15}-phenyl, R^{15}-benzyl, -NO_2, -$NR^{11}S(O)_2R^{13}$ and -$S(O)_2NR^{11}R^{12}$; or adjacent R^1,

15 R^3 or R^4 substituents can form a -O-CH_2-O- group;

R^2 is independently selected from the group consisting of R^{2a}, R^{2b} or R^{10}; and R^{2c} is independently selected from the group consisting of R^{2a} and R^{10}; wherein R^{2a} is selected from the group consisting of -CF_3, -C_2F_5, -COR^{11}, -CO_2R^{11}, -$CON(R^{11})(R^{12})$, R^{15}-phenyl

20 and R^{15}-benzyl; and R^{2b} is selected from the group consisting of halogeno, -OR^{11}, -NO_2, -$N(R^{11})(R^{12})$, -$N(R^{11})COR^{12}$, -SH, -$S(O)_eR^{13}$, -$OC(O)R^{11}$, -$OC(O)N(R^{11})(R^{12})$, -$NR^{11}CO_2R^{13}$, -$NR^{11}C(O)N(R^{12})(R^{14})$, -$NR^{11}S(O)_2R^{13}$ and -$S(O)_2NR^{11}R^{12}$; provided that from any combination of ring members A^1, A^2, A^3 and A^4 comprising R^2 and R^{2c}, no more than

25 one substituent can be selected from R^{2a} and no more than one substituent can be selected from R^{2b};

R^5, R^7, R^9, R^{11}, R^{12} and R^{14} are independently selected from the group consisting of H, C_1-C_6 alkyl, R^{15}-phenyl, R^{15}-benzyl, -CF_3 and -C_2F_5;

30 R^6 and R^8 are independently selected from the group consisting of R^5, -$(C(R^9)(R^{10}))_n$-OR^{11}, -$(C(R^9)(R^{10}))_n$-$NR^{11}R^{12}$, -$(C(R^9)(R^{10}))_n$-SH, -$(C(R^9)(R^{10}))_n$-$S(O)_eR^{13}$, -$(C(R^9)(R^{10}))_n$-CO_2R^{11}, -$(C(R^9)(R^{10}))_n$-$OC(O)R^{11}$, -$(C(R^9)(R^{10}))_n$-$CONR^{11}R^{12}$, -$(C(R^9)(R^{10}))_n$-COR^{11} and -$(C(R^9)(R^{10}))_n$-$NR^{11}C(O)R^{12}$, provided that

35 when Q is a heteroatom, R^6 and R^8 cannot be -OR^{11}, -$OC(O)R^{11}$, -$N(R^{11})COR^{12}$, -$NR^{11}R^{12}$, -SH or -$S(O)_eR^{13}$ on adjacent carbon atoms;

R^{10} is independently selected from the group consisting of hydrogen and C_1-C_6 alkyl;

R^{13} is independently selected form the group consisting of C_1-C_6 alkyl, R^{15}-phenyl, R^{15}-benzyl, -CF_3 and -C_2F_5;

R^{15} is hydrogen, C_1-C_6 alkyl, C_1-C_6 alkoxy or halogeno;

Q is a bond, -C(O)-, -NR^{17}-, -$(C(R^9)(R^{10}))$-, -O-, -$S(O)_e$-, -C(X)NR^{11}-, -N(R^{11})C(X)-, -N(R^{11})SO_2-, -SO_2N(R^{11})- or -N+(R^{11})(R^{17})-;

R^{16} and R^{17} are independently selected from the group consisting of hydrogen, C_1-C_6 alkyl, -$S(O)_eR^{13}$, -COR^{11}, -$(CH_2)_m$-CO_2R^{13}, -$CONR^{11}R^{12}$, C_2-C_6 alkenyl, -R^{15}-phenyl and R^{15}-benzyl;

X is =O, =S or =N(R^{12});

Y^1 is -$(C(R^9)(R^{10}))_m$-, -G-$(C(R^9)(R^{10}))_m$- or -$(C(R^9)(R^{10}))_m$-G-;

G is

, provided that when m is 0, R^2 is H, C_1-C_6 alkyl, -CF_3, -C_2F_5, -COR^{11}, -CO_2R^{11}, -CON(R^{11})(R^{12}), R^{15}-phenyl or R^{15}-benzyl;

, provided that when p is 0, T is not OH or -$NR^{11}R^{12}$;

, provided that when r is 1, T is not OR^{11} or -$NR^{11}R^{12}$; or

, provided T is not -OR^{11}, -N(R^{11})(R^{12}), -$S(O)_eR^{13}$, -$NR^{11}CO_2R^{13}$, -$NR^{11}COR^{12}$, -$NR^{11}CON(R^{12})(R^{14})$ or -$OC(O)N(R^{11})(R^{12})$;

T is H, R^{15}-aryl, R^{15}-heterocycloalkyl, R^{15}-heteroaryl, R^{15}-cycloalkyl, -OR^{11}, -N(R^{11})(R^{12}), -COR^{11}, -CO_2R^{11}, -CON(R^{11})(R^{12}), -$S(O)_eR^{13}$, -$NR^{11}CO_2R^{13}$, -$NR^{11}COR^{12}$, -$NR^{11}CON(R^{12})(R^{14})$ or -$OC(O)N(R^{11})(R^{12})$;

J is a bond, -$S(O)_e$-, -O- or -N(Z^2)-, -N(Z^2)C(O)- or -N(Z^2)C(S)-; and when G is -C(R^2)H-, J can also be -N(Z^2)C(O)O- or -OC(O)N(Z^2)-;

Y^2 is -$(C(R^9)(R^{10}))_m$-;

Z^1 is H, C_1-C_6 alkyl, R^{15}-phenyl, R^{15}-benzyl, -CF_3, -C_2F_5, -$NR^{11}R^{12}$, -OR^{11} or SR^{11}; Z^2 is H, C_1-C_6 alkyl, R^{15}-phenyl, R^{15}-benzyl, -CF_3 or -C_2F_5; provided that when Y^1 is -$(C(R^9)(R^{10}))_m$- and m is 0, Z^1 is not -$NR^{11}R^{12}$, -OR^{11} or -SR^{11}; or Z^1 and Z^2 together are -$(C(R^9)(R^{10}))_u$-,

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wherein u is 1 to 4, and wherein with the atoms to which they are attached, form a 4 to 8 membered ring;

> e and n are independently 0, 1 or 2;
> m and p are independently 0, 1, 2 or 3; and
> r and s are independently 1, 2, 3 or 4.

2.   A compound of claim 1 wherein E is R^3-phenyl.

3.   A compound of claim 1 or 2 wherein Z^1 is hydrogen, or Z^1 and Z^2 together are ethylene or propylene, and with the atoms to which they are attached form a 5- or 6-membered ring.
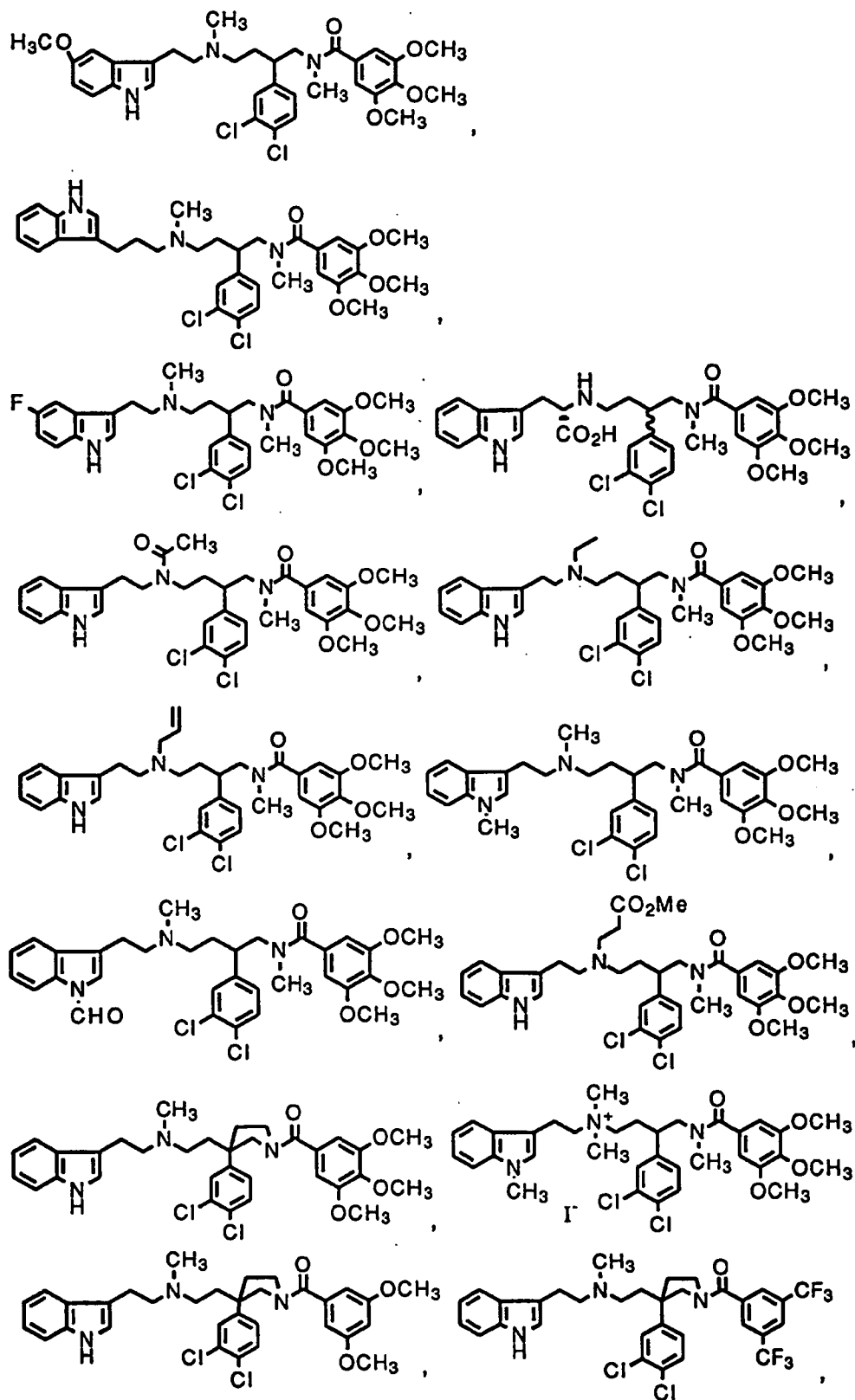
4.   A compound of any of claims 1, 2 or 3 wherein Q is $-NR^{17}-$, -O- or $-S(O)_e-$.

5.   A compound of any of claims 1, 2, 3 or 4 wherein J is -O-, $-N(Z^2)-$ or $-N(Z^2)C(O)-$.

6.   A compound of any of claims 1, 2, 3, 4 or 5 wherein A^1, A^2, A^3 and A^4 comprise an indolyl ring.
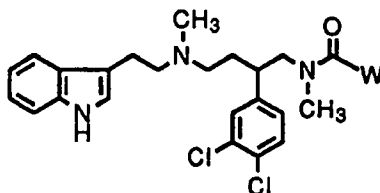
7.   A compound of claim 1 selected from the group consisting of
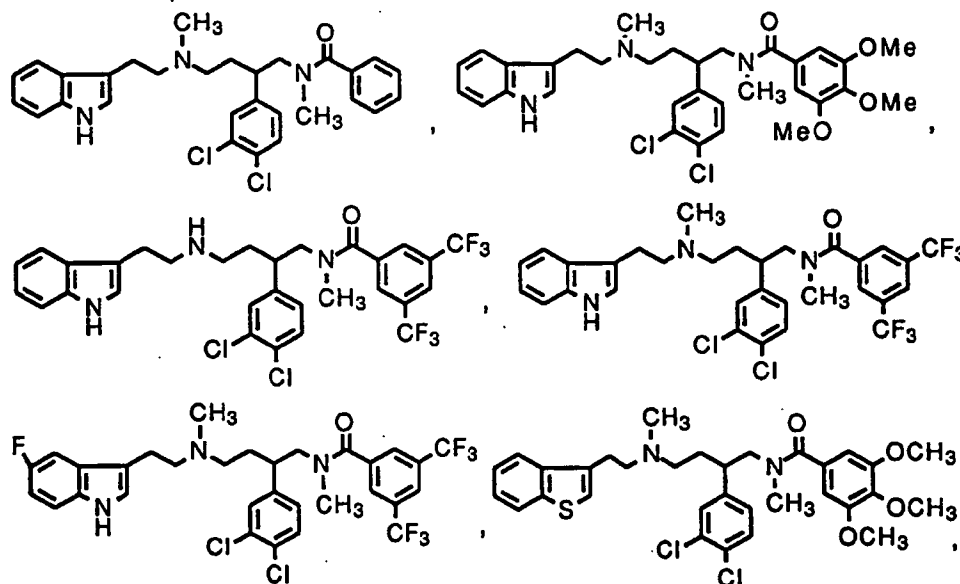
and a compound of the formula

wherein W is
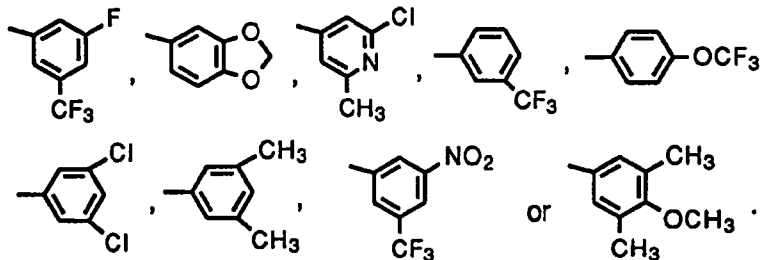
8.   A pharmaceutical composition comprising an effective amount of a compound of any of claims 1, 2, 3, 4, 5, 6 or 7 in a pharmaceutically acceptable carrier.

9.   The use of a compound of any of claims 1, 2, 3, 4, 5, 6 or 7 for the preparation of a medicament for the treatment of asthma, cough, bronchospasm, central nervous system diseases, inflammatory diseases and gastrointestinal disorders.

10.   A method of treating asthma, cough, bronchospasm, central nervous system diseases, inflammatory diseases and gastrointestinal disorders comprising administering an effective amount of a compound of any of claims 1, 2, 3, 4, 5, 6 or 7 to a mammal in need of such treatment.

INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6   C07D209/16   A61K31/40   C07D333/58   C07D403/12   C07D209/20
         C07D405/12   C07D401/12   C07D215/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6   C07D   A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A,5 350 852 (SANOFI) 27 September 1994 cited in the application see claims	1,8,9
A	EP,A,0 591 040 (ELF SANOFI) 6 April 1994 see claims	1,8,9
A	WO,A,93 18023 (MERCK SHARP & DOHME LTD.) 16 September 1993 see claims	1,8,9

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

'A' document defining the general state of the art which is not considered to be of particular relevance

'E' earlier document but published on or after the international filing date

'L' document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

'O' document referring to an oral disclosure, use, exhibition or other means

'P' document published prior to the international filing date but later than the priority date claimed

'T' later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

'X' document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

'Y' document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

'&' document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 August 1996	2 0. 08. 96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Van Bijlen, H

Form PCT/ISA/210 (second sheet) (July 1992)

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INTERNATIONAL SEARCH REPORT

Box I   Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
   because they relate to subject matter not required to be searched by this Authority, namely:

   Remark:Although claim 10 is directed to a method of treatment of (diagno-
   stic method practised on) the human/animal body, the search has been
   carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
   because they relate to parts of the international application that do not comply with the prescribed requirements to such
   an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II   Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all
   searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment
   of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report
   covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is
   restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest   [ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1992)

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US-A-5350852	27-09-94	FR-A-	2666335	06-03-92
		FR-A-	2678267	31-12-92
		AU-B-	657272	09-03-95
		AU-B-	8354291	12-03-92
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		EP-A-	0474561	11-03-92
		IL-A-	99320	31-07-95
		JP-A-	4261155	17-09-92
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